Recommendations for prescription of oral anti-inflammatory agents in oral surgery in adults

**FRENCH-SPEAKING SOCIETY OF ORAL MEDICINE
AND ORAL SURGERY**

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GENERAL METHODOLOGY

Objective

Anti-inflammatory drugs are widely prescribed in oral surgery, but many instances of controversy or confusion still exist (indications, choice of compound, dosage, duration of treatment, precautions for use, drug interactions, contraindications, adverse events, risk of infection related to use of an anti-inflammatory drug). This sometimes results in an erroneous, insufficient or imprecise prescription where the risk of adverse events is greater than the benefit provided to the patient. In an attempt to provide a response to these different instances of controversy or confusion, the SFMbCb has asked a working group to formulate recommendations for the prescription of anti-inflammatory drugs in oral surgery.

Questions asked to the working group

1. What are the indications for anti-inflammatory drugs and the compounds to use?
2. What are the modalities for prescribing anti-inflammatory drugs?
3. What are the adverse events, precautions for use and contraindications for anti-inflammatory drugs?
4. Do anti-inflammatory drugs promote infection and do they justify prescription of antibiotics?

Bibliographical search criteria
Languages
1. French
2. English

Limits
1. Primarily recent publications (last 10 years) have been used but reference is also made to a few older publications which reported a discovery or a new approach.

2. Studies conducted in humans.

Search (database)
1. AFSSAPS (French National Agency for the Safety of Medicines and Health Products)
2. ANAES (French National Agency for Accreditation and Evaluation of Health)
3. Bibliodent
4. Libraries
5. Cochrane
6. Embase
7. EMC (French Medical Surgical Encyclopaedia)
8. HAS (French National Authority for Health)
9. Internet
10. Medline
11. Pascal
12. SFMbCb (French-Speaking Society of Oral Medicine and Oral Surgery)

MeSH (key words)
1. Non-steroidal anti-inflammatory drug
2. Corticosteroid therapy
3. Dental care
4. Non-steroidal anti-inflammatory drug
5. Oral surgery
6. Periodontal surgery
7. Tooth extraction
8. Dental extraction

Medical journals (systematic study of summaries of medical journals)
1. British Dental Journal
2. International Journal of Oral and Maxillofacial Surgery
3. Journal of Clinical Pharmacology
4. Journal of Craniomaxillofacial Surgery 5. Journal of Oral and Maxillofacial Surgery 6. Journal of Dental Research
7. Médecine Buccale Chirurgie Buccale
8. Oral Surgery Oral Medicine Oral Pathology Oral Radiology and Endodontology
9. Revue Prescrire
10. Revue de Stomatologie et de Chirurgie Maxillo-Faciale

Methodology

For the formulation and writing of a reasoned argument and recommendations the methodology proposed by AFSSAPS has been followed. Each bibliographical reference has been analysed by assessing its methodological quality in order to assign a level of scientific evidence scored from 1 to 4 to each reference. Recommendations are classified according to their strength in grades (A, B or C) taking into account the level of evidence of the studies on which they are based.

Level of scientific evidence provided by the literature (therapeutic studies)		Grade of recommendations
Level 1	High power randomised comparative trials Meta-analysis of randomised comparative trials Analysis of decision based on well-conducted studies	**A** Established scientific evidence
Level 2	Low power randomised comparative trials Well-conducted non-randomised comparative studies Cohort studies	**B** Scientific presumption
Level 3	Case control studies	
Level 4	Comparative studies containing major bias Retrospective studies Case series Descriptive epidemiological studies (cross-sectional, longitudinal)	**C** Low level of scientific evidence

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Warning

Salicylates and NSAIDs belong to the same therapeutic class (antipyretic-analgesic agents) but it is necessary to differentiate these two classes of medicinal products. In fact, their pharmacological properties are very different, mainly due to the fact that salicylates (in particular aspirin) are irreversible cyclo-oxygenase inhibitors. Therefore, the action of aspirin is directly related to turnover of cyclo-oxygenases in tissue. This explains in particular why aspirin has an extended action on primary haemostasis: it irreversibly inhibits the adhesion of platelets affected.

NSAIDs have their principal indication as anti-inflammatory agents in treatment of certain musculoskeletal disorders (rheumatoid arthritis, osteoarthritis, etc.). Most often, NSAIDs enable only a decrease in symptoms of inflammation and pain caused by these disorders but they cannot by themselves stop progression of the disorder. The anti-inflammatory effect then involves reduction of super-oxide radicals and induction of apoptosis, inhibits the expression of adhesion molecules, decreases the synthesis of NO synthetase and of pro-inflammatory cytokines. These effects can be observed only at high doses and after one to two weeks of treatment.

RECOMMENDATIONS

Introduction

Anti-inflammatory agents contain two classes of medicinal products: non-steroidal anti-inflammatory drugs or NSAIDs and glucocorticoids. They have different properties which are not well-known or are poorly known. Some of them have entered into everyday practice by use and self-medication; others, in particular glucocorticoids, raise concern and fear which, in reality, this is based on out-of-date notions. Several recent studies have enabled us to better understand their mode of action, to look for and to discover new compounds reputed to have fewer adverse events, and to demonstrate rare but real side effects. The purpose of these recommendations is to offer a consistent approach for the prescription of anti-inflammatory agents in oral surgery based on a reasoned analysis of data from the literature and expert opinion. They are aimed at dental surgeons, stomatologists, maxillofacial surgeons, general practitioners, specialists (otolaryngologists, internists, anaesthesiology intensive care specialists, etc.) and pharmacists.

For practical reasons, particularly legibility, recommendations for NSAIDs and those for glucocorticoids will be presented separately, even though this appears to be redundant as the questions raised are common to the two classes of medicinal products.

The salicylates (aspirin, etc.) have been excluded from these recommendations as a result of their effect on coagulation and anti-inflammatory agents for a particular purpose (e.g. colchicine etc.) which are not indicated in oral surgery.

NSAIDs in oral surgery

Indications

1. The analgesic effect of NSAIDs is greater than that of paracetamol and is comparable to that of weak opioids (codeine, tramadol, etc.) used alone or in combination with paracetamol (grade A). On the contrary, NSAIDs do not have an effect that is superior to paracetamol alone on other inflammatory symptoms (oedema and trismus). **In oral surgery, NSAIDs therefore must not be considered to be anti-inflammatory agents but solely as analgesics** (grade A).

2. It is recommended that NSAIDs be used with an MA obtained for the indication analgesia (Tab.1). Among the 9 compounds which have marketing authorisation (fenamates: mefenamic acid and niflumic acid, propionic acid, ibuprofen, tiaprofenic acid, fenoprofen, ketoprofen and naproxen; and other agents: diclofenac and nimesulide), none has demonstrated its superiority compared to the others, in terms of efficacy and safety (professional agreement).

Table 1: List of NSAIDs which have an MA with the indication for analgesia (Vidal 2008®).

INN	Trade name	Dosage	Dosage per dose	Daily maximum dose
Mefenamic acid	Ponstyl®	250 mg	250 to 500 mg	1,500 mg
Niflumic acid	Nifluril®	250 mg	250 mg	1,000 mg
Ibuprofen	Advil®, generic drugs	200, 400 mg	200 to 400 mg	1,200 mg
Tiaprofenic acid	Surgam®, Flanid®	100, 200 mg	100 to 200 mg	600 mg
Fenoprofen	Nalgesic®	300 mg	300 to 600 mg	1,200 mg
Ketoprofen	Toprec®	25 mg	25 mg	75 mg
Naproxen	Aleve®, Apranax®, generic drugs	220, 275, 500, 750 mg	220, 275, 500, 750 mg	1,100 mg
Diclofenac	Voltarene Dolo®	12.5 mg	12.5 to 25 mg	75 mg
Nimesulide	Nexen®	100 mg	100 mg	200 mg

Prescribing modalities

3. Prescription of an NSAID for analgesic purposes must comply with principles of the therapeutic strategy for management of pain. The use must be preventive and the product administered at a set time: as first-line therapy, prescription "in the event of pain" is not recommended (see Prevention and treatment of post-operative pain in oral surgery. HAS 2005) (grade A).

4. Initial management must take into account time to onset of action (about 1 hr. for an oral dose) of the compound to obtain efficacy before the foreseeable end of local or locoregional anaesthesia (see Prevention and treatment of post-operative pain in oral surgery, HAS 2005) (grade A).

5. Optimum duration of treatment for analgesic purposes is 3 days. In principle, it must not exceed 5 days; persistence of pain without decrease in its intensity must lead to a re-evaluation of the case (professional agreement).

6. Administration by oral route must be preferred for procedures under local and locoregional anaesthesia (grade A).

Contraindications

7. The prescription of an NSAID must take into account its adverse events, the precautions for use and contraindications. It must be avoided in patients presenting a contraindication: pregnancy over a term of 5 months or breastfeeding mothers, the elderly (> 65 years of age), subjects presenting with an ulcer disease, even if cured or gastrointestinal inflammatory in nature, subjects with renal impairment (creatinine clearance < 60 ml/min), patients under treatment with an anti-coagulant, treatment with a platelet anti-aggregant, a coagulation disorder (grade A).

8. It is contraindicated to use two NSAIDs at effective dose in combination (see Prevention and treatment of post-operative pain in oral surgery, HAS 2005) (professional agreement).

Do NSAIDs increase the risk of infection?

9. The cause-effect relationship between intake of an NSAID and an increase in risk of infection is not scientifically established in oral surgery. However, practitioners are reminded that use of an NSAID may mask the signs of infection. Prescription of an NSAID does not by itself justify prescription of an antibiotic (professional agreement).

10. Prescription of antibiotics retains its indications independently of prescription of NSAIDs (see Prescription of antibiotics in Odontology and in Stomatology. AFSSAPS 2001) (grade A).

Glucocorticoids in oral surgery

Indications

1. Glucocorticoids (Tab. 2) are indicated for prevention of inflammatory manifestations (oedema and trismus) (professional agreement).

2. Their modest analgesic activity justifies the concomitant prescription of analgesic agents. Combination with an NSAID is not advisable (grade A).

3. Glucocorticoid, by acting on the inflammatory component, may prevent post-operative neuropathic pain (professional agreement).

4. Analysis of the literature concerning oral surgery does not make it possible to prefer one compound among all those available on the market. For pharmacokinetic reasons (bioavailability, biological half-life), it appears preferable to use prednisone (professional agreement).

Prescribing modalities

5. Initial administration must take into account the time to action of glucocorticoids to obtain efficacy before start of the procedure (at least 4 hours before the procedure for an oral dose). Conventionally, it is given in the morning of the day before the procedure (professional agreement).

6. The recommended mean daily dose is 1 mg/kg body weight equivalent in prednisone equivalent, OD in a single dose in the morning (professional agreement).

7. The optimum duration of treatment is 3 days, with a maximum of 5 days (professional agreement); since this involves short courses of therapy, treatment is discontinued without having to progressively decrease the dose (grade A).

8. For all procedures under local or loco-regional anaesthesia, administration by mouth must be preferred; intramuscular injection is not advisable because of the risk of infection related to the injection (professional agreement).

Contraindications

9. Prescription of glucocorticoids must take into account their adverse events, their precautions for use and their absolute contraindications (viral diseases and other ongoing infections, uncontrolled psychosis, etc.) and relative (diabetes, immune deficiency, etc.) (professional agreement).

Do glucocorticoids, in short courses of therapy, increase the risk of infection?

10. Prescription of glucocorticoids in a short course of therapy does not by itself justify prescription of antibiotics; the cause-effect relationship between use of glucocorticoids in a short course of therapy and an increase in risk of infection is not scientifically established in oral surgery. However, it may reveal a latent infection (tuberculosis, etc.) (professional agreement).

Table 2: Trade names of glucocorticoids marketed in France

INN	Trade name	Form	Dosage	Loading dosage (oral route)
Betamethasone phosphate disodium	Betnesol®	Oral Parenteral	0.5 mg 4 mg/ml	0.05 to 0.2 mg/kg/day
Betamethasone	Celestene®	Oral	0.5 mg, 2 mg	0.05 to 0.2 mg/kg/day
Betamethasone acetate	Celestene Chronodose®	Intramuscular	5.7 mg/ml	1 injection during the allergy period
Dexamethasone acetate	Dectancyl®	Oral	0.5 mg	0.05 to 0.2 mg/kg/day
Dexamethasone phosphate sodium	Dexamethasone Merck®	Parenteral	4 mg/ml	2 to 20 mg/day
Methylprednisolone acetate	Depo-Medrol®	Intramuscular	40 mg/ml	1 injection during allergy period
Methylprednisolone	Medrol®	Oral	4, 16, 32, 100 mg	0.3 to 1 mg/kg/day
Methylprednisolone succinate sodium	Methylprednisolone Dakotapharma®	Parenteral	10 mg/ml, 60 mg/ml	120 mg/day
Methylprednisolone	Methylprednisolone Merck®	Parenteral	20 mg, 40 mg, 500 mg, 1g	120 mg/day
Prednisolone acetate	Hydrocortancyl®	Local (injection)	125 mg/5ml	1/2 to 2 ml depending on site of injection and disorder to be treated
Prednisolone	Hydrocortancyl®	Oral	5 mg	0.35 to 1.2 mg/kg/day
Prednisolone metasulfobenzoate sodium	Solupred®, generic drugs	Oral	1 mg/ml, 5 mg, 20 mg	0.35 to 1.2 mg/kg/day
Prednisone	Cortancyl®	Oral	1, 5, 20 mg	0.35 to 1.2 mg/kg/day

11. Prescription of antibiotics in oral surgery retains its indications independently of prescription of glucocorticoids

(see Prescription of antibiotics in Odontology and Stomatology, AFSSAPS 2001) (grade A).

In oral surgery:
· NSAIDs must be considered solely as analgesics because they have no effects on œdema and trismus.
· Optimum management of inflammatory manifestations (pain, œdema, trismus) is based on the combination use of a glucocorticoid and of a non-inflammatory analgesic agent (paracetamol, codeine, tramadol) [17,75,86,87,97,109,117,120,133,138].
· The combination of a glucocorticoid and an NSAID is not advisable.

ARGUMENT

In oral surgery, procedures are very frequently associated with a loco-regional inflammatory process. Control of this process primarily involves prescription of anti-inflammatory and analgesic agents. The purpose of this report is to provide an update on the indications and contraindications of prescription of anti-inflammatory agents in oral surgery. Practically speaking, this report should clarify for the practitioner the choice of a compound to be used, dosage, duration, adverse events and contraindications of the treatment.

1. Pharmacological data

1.1. General aspects

Oral surgery causes trauma to the tissue, which triggers a local acute inflammatory process. It is a beneficial physiological process which promotes detersion, elimination of lesional tissue and healing[42]. This process is manifest clinically by four cardinal signs: pain, warmth, oedema and erythema, which correspond to the first phase or vascular haematological phase of inflammation. Trismus can also occur during the days following the procedure. The seriousness of these post-operative events reaches its apex 2 to 3 days after the procedure on average. Their precise duration is poorly understood; undoubtedly, it varies from one patient to another and depends on type of surgery. According to Laskin (1985) [70], maximum oedema may be observed at

between 14 and 48 hours post-surgery, while according to Peterson[94] this period should be between 48 and 72 hours. In all cases, oedema regresses before the end of the first post-operative week, with or without treatment with glucocorticoids[5].

Clinical symptoms are explained by fluid and cellular events which comprise the inflammatory reaction. Active congestion is characterised by vasodilation, which occurs very quickly after a short phase of vasoconstriction; it corresponds to arteriolar and then capillary vasodilation in the affected area. Locally, an increase in blood flow results with a decrease in circulatory rate. Inflammatory oedema is formed by passage into the interstitial connective tissue of an exudate consisting of water and plasma proteins. An increase in hydrostatic pressure results from this due to vasodilation and in particular an increase in permeability of the small vessel wall under the effect of chemical mediators, in particular that of histamine. Then, migration of leucocytes occurs outside of the microcirculation and they accumulate in the area of the lesion. From 6 to 24 hours, this migration involves, first, the neutrophils, and then from 24 to 48 hours the monocytes and lymphocytes.

The role of inflammation in the aetiogenesis of post-operative pain is dominant. During this phase, various substances, the majority of which are neuro-active (Fig. 1), will be synthesised, forming an "inflammatory mixture"[72]. These substances mainly have three origins: lesional cells (release of ATP and of protons),
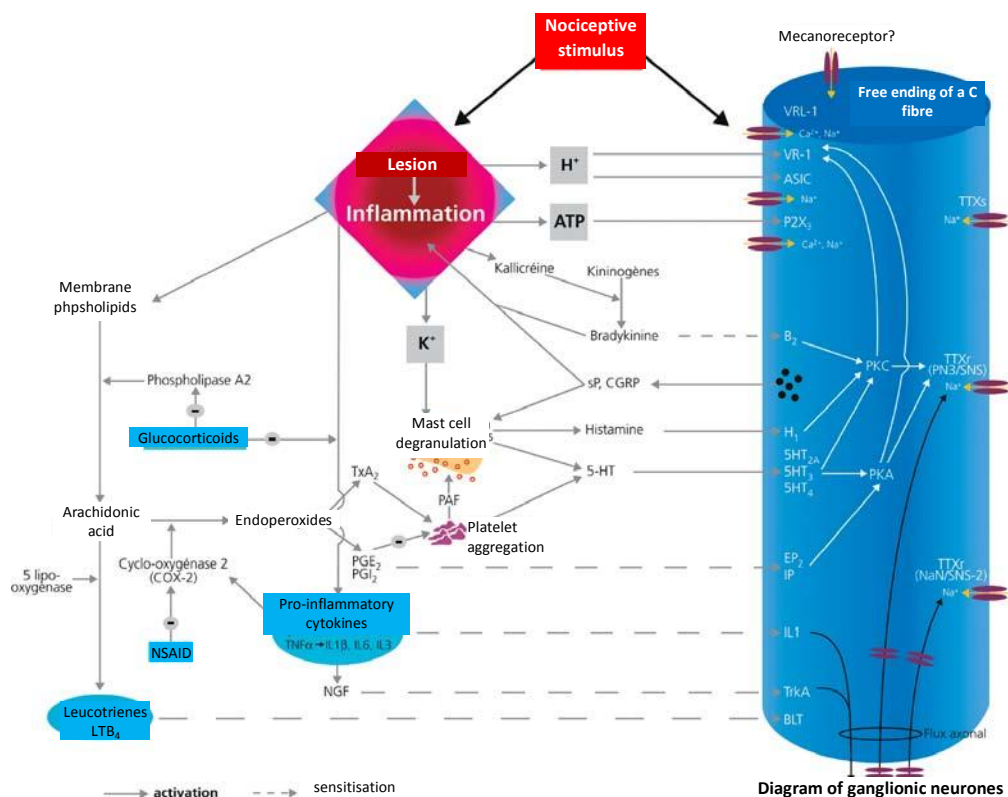
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Figure 1: Mediators of inflammation that can activate or sensitise nociceptors after a tissue lesion (from [72]). This figure represents factors that can activate (———▶) and/or sensitise (------▶) the nociceptors after a tissue lesion. 5-HT: 5-hydroxytryptamine (serotonin); ADP: adenosine diphosphate; ASIC: acid-sensing ionic channel; ATP: adenosine triphosphate; BK: bradykinin; CB: cannabinoid receptor; CCK: cholecystokinin; CGRP: calcitonin gene-related peptide; COX: cyclo-oxygenase; EP: prostaglandin E receptor (PGE); GDNF: glial cell-derived neurotrophic factor; IL: interleukin; PGI: prostaglandin I receptor; NGF: nerve growth factor; P1: purinergic receptor 1 = adenosine; P2: purinergic receptor 2 = ATP; P2X: ionotropic receptor to ATP; P2Y: metabotropic receptor to ATP; PAF: platelet activating factor; PAR: protease-activated receptors; PG: prostaglandin; PKA: protein-kinase A; PKC: protein-kinase C; PLC: phospholipase C; SP: substance P; TTXr: sodium channels resistant (insensitive) to tetrodotoxin; TTXs: sodium channels sensitive to tetrodotoxin; VDCC: voltage-dependent calcium channel; VGSC: voltage-gated sodium channel; VIP: vasoactive intestinal peptide; VR: vanilloid receptor; VRL: vanilloid receptor-like.

inflammatory cells (histamine and serotonin) and nociceptors themselves. Prostaglandin synthesis from arachidonic acid is triggered in cells exposed to pro-inflammatory agents.

The physiological effects of tissue trauma can be effectively limited by two major classes of medicinal products: synthetic glucocorticoids and non-steroidal anti-inflammatory agents. They must be differentiated because they differ in their mechanisms of action, their indications, their adverse events and their contraindications.

1.2. Non-steroidal anti-inflammatory agents

1.2.1. Pharmacology of NSAIDs – Mechanism of action

The NSAIDs represent a class of medicinal products that differ from each other from a chemical standpoint, but that are very similar from a pharmacological standpoint (mechanism of action, adverse events, contraindications, etc.) [6,12,108]. Their principal pharmacodynamic property consists of inhibiting the activity of cyclo-oxygenases (COX) that are essential to prostaglandin synthesis. Cyclo-oxygenases (or prostaglandin G/H synthetases)

are bi-functional proteins that possess a first cyclo-oxygenase action on arachidonic acid which they convert into prostaglandin G2, and then a hydroperoxidase activity, enabling conversion of prostaglandin G2 into prostaglandin H2 (Fig. 2) [48,80]. Depending on tissue and cell type where primary prostaglandins are produced, they are metabolised by specific isomerases and synthetases in the tissue into different forms of prostaglandins and into thromboxane A2. All these compounds act subsequently by activating receptors with seven transmembranal domains, coupled with protein G.

Two isoforms of COX (COX-1 and COX-2) which have a different structure, mechanism of expression and function have been demonstrated.

COX-1 and 2 have a structural homology of about 60%. Their difference in structure explains the nature of interactions with different ligands and the possiblity of interaction with larger molecules would be at the origin of the specific inhibition action of COX-2 by some anti-inflammatory agent so-called "COX-2 selective inhibitors or coxibs" [8,26,38,62,64,65,80,88,95,107,144]. Since the active site of COX-2 is larger than that of COX-1, it can accept molecules that have the same structure as conventional NSAIDs (non-selective inhibitors) but which have an additional group. This structural difference is at the origin of the selectivity of some compounds (coxibs) for COX-2.
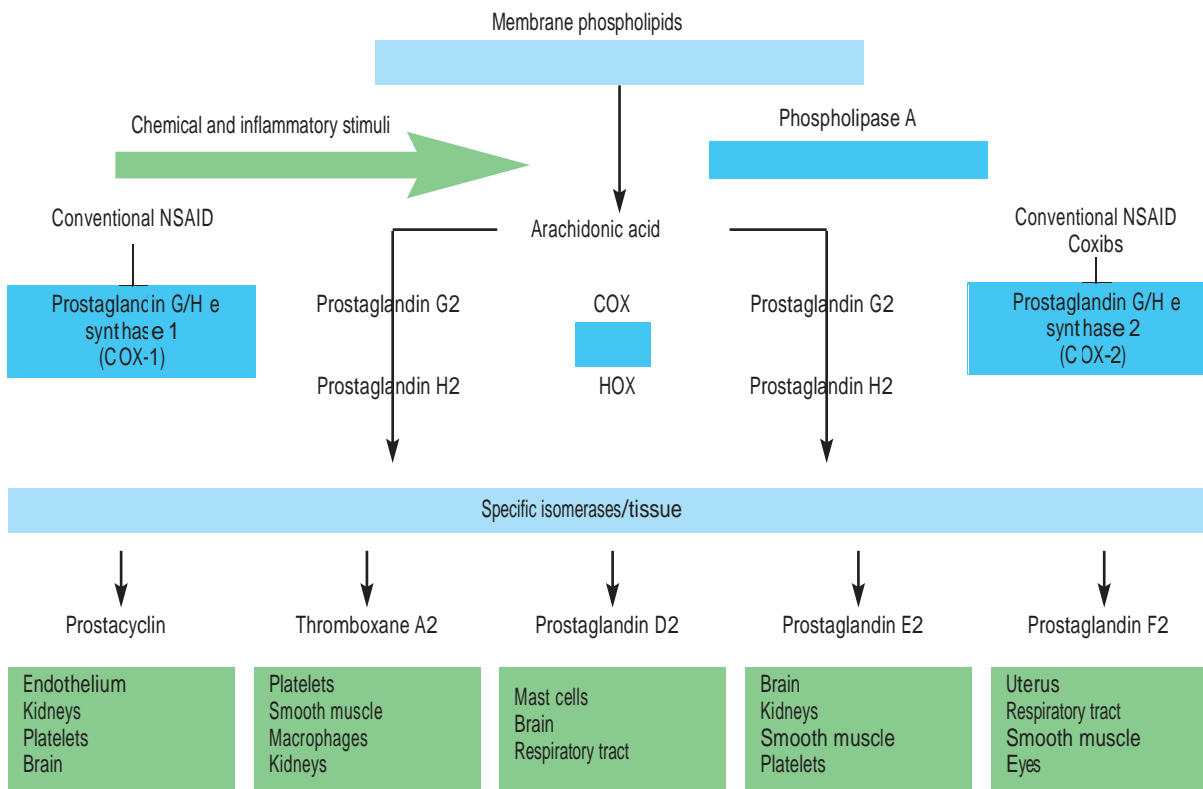
Figure 2: Synthesis of different prostaglandins from arachidonic acid (from [38]). (COX: cyclo-oxygenase, HOX: hydroperoxidase).

Differences also exist in the method and diagram of expression of COX. COX-1 is a component enzyme expressed in the majority of tissues, excepting (among others) in the central nervous system. It participates in many physiological processes: arterial vasodilation, platelet aggregation, bronchial dilation, decrease in gastric acidity, increase in secretion of gastric mucus etc. Expression of COX-2 is more complex: initially considered inducible, it may be a component of certain tissues, such as the GI tract, brain or kidney. It is induced primarily by the inflammatory process, manifest by an increase in its rate of expression in inflammatory tissue. Synthesis of prostaglandins (PGE2) by COX-2 is responsible for the sensitisation of nociceptors resulting in primary hyperalgesia. Lastly, it has been shown that inflammation is responsible for induction of COX-2 in the bone marrow and in some areas of the central nervous system [107]. Therefore, both by their capacity to inhibit the activity of COX and therefore synthesis of PGE2, PGI2 and of thromboxane A2, NSAIDs have four essential pharmacological properties: anti-inflammatory activity, analgesic activity, antipyretic activity and action on platelet aggregation (Fig. 3). These different properties, common to all NSAIDs, are modulated depending on the active substance and duration of treatment. It should be noted that selective inhibitors of COX-2 seem to have different actions on platelet aggregation which have led to the withdrawal of certain coxibs from the market.

1.2.2. Classification and criteria for choice in oral surgery

Contrary to the glucocorticoids, NSAIDs have a high variability of chemical structure, upon which their classification is based. Many compounds currently have an MA in France[6]. Two indications are established primarily: first, symptomatic treatment of acute or chronic rheumatic disorders (chronic inflammatory rheumatism), and also symptomatic treatment of painful disorders of mild to moderate seriousness and/or that of febrile conditions. From a strictly regulatory standpoint only, nine compounds in France have an MA for the analgesia indication with precise dosages (Tab. 1). This involves mefenamic acid, niflumic acid, ibuprofen, tiaprofenic acid, fenoprofen, ketoprofen, naproxen, diclofenac, and nimesulide. The majority of these NSAIDs belong to two classes: fenamates (mefenamic acid and niflumic acid) and propionic acid (ibuprofen, tiaprofenic acid, fenoprofen, ketoprofen and naproxen). They have a certain number of common characteristics. Their selectivity for COX rather than for another enzyme is little confirmed: they are non-selective inhibitors (diclofenac and nimesulide would appear to be more selective for COX-2, ketoprofen for COX-1) [144]. Each of these compounds has a short elimination half-life (2 hours on average, except for naproxen which is 13 hours) and relatively low GI toxicity for the majority of them compared to other classes of NSAID. It should be noted that only two NSAIDs (naproxen or Apranax® and tiaprofenic acid or Surgam® and Flanid Gè®) have a specific indication for our activity: "short term symptomatic treatment of pain in inflammatory manifestations in stomatology" (Vidal 2008®).

1.3. Glucocorticoids

1.3.1. Definition

The natural corticosteroids, synthesised by the adrenal glands, present either a dominant glucocorticoid activity, like cortisol, or a dominant mineralocorticoid activity, like aldosterone. Starting from cortisol, glucocorticoid derivatives have been synthesised, their duration of action is longer, their anti-inflammatory activity is greater and their mineralocorticoid activity is lower than that of the parent compound (cortisol).

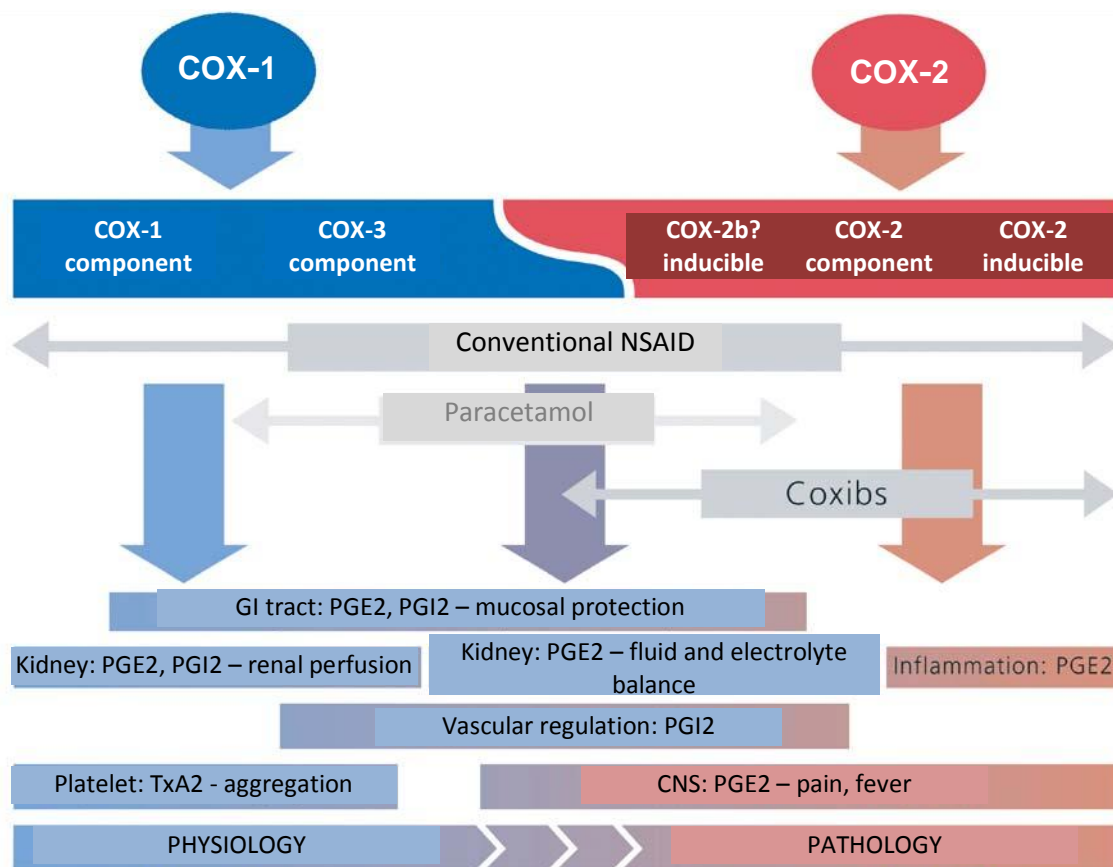The glucocorticoids have structural homogeneity. They are steroid hormones

Figure 3: Diversity of expression for COX and targets of NSAID (from [143]).
(COX: cyclo-oxygenase; PG: prostaglandin; TxA2: thromboxane A2; CNS: central nervous system).

Table 1: List of NSAIDs that have an MA with analgesia as the indication (Vidal 2008®).

INN	Medicinal product	Dosage	Dosage per dose	Maximum daily dose
Mefenamic acid	Ponstyl®	250 mg	250 to 500 mg	1,500 mg
Niflumic acid	Nifluril®	250 mg	250 mg	1,000 mg
Ibuprofen	Advil®, generic drugs	200, 400 mg	200 to 400 mg	1,200 mg
Tiaprofenic acid	Surgam®, Flanid®	100, 200 mg	100 to 200 mg	600 mg
Fenoprofen	Nalgesic®	300 mg	300 to 600 mg	1,200 mg
Ketoprofen	Toprec®	25 mg	25 mg	75 mg
Naproxen	Aleve®, Apranax®, generic drugs	220, 275, 500, 550 mg	220, 275, 500, 550 mg	1,100 mg
Diclofenac	Voltarene Dolo®	12.5 mg	12.5 to 25 mg	75 mg
Nimesulide	Nexen®	100 mg	100 mg	200 mg

with 21 carbon atoms. They are used mainly in treatment for their anti-inflammatory properties [19,20,35,43] and immunosuppressant properties. Other properties are generally responsible for their adverse events.

1.3.2. Mechanism of action

The mechanism of action of the glucocorticoids involves mainly a transcriptional action on target genes [28,35,102,128]. Only the unbound fraction of glucocorticoids (10 to 20%) is responsible for the pharmacological activity. They act, after being associated with their intracytosolic receptor, by binding to the specific region of the promoter (GRE) of their target gene. Therefore, they activate the synthesis of anti-inflammatory proteins such as lipocortin 1 (an inhibitor of A2 phospholipases), interleukin 10 or protein IkB. The anti-inflammatory action of glucocorticoids is also manifest by interaction with other factors of transcription. Formation of a glucocorticoid-receptor complex with protein AP1 enables inhibition of many collagenases and pro-inflammatory cytokines. Similarly, the combination with transcription factor NF-kB inhibits the synthesis of COX-2, which is essential for production of prostaglandins. Glucocorticoids also have therapeutic effects which do not involve specific receptors. They may result in phosphorylation of annexin-1 which may modify the function of enzymes, in particular the metabolism of cyclical AMP.

Glucocorticoids will therefore produce inhibition of all soluble mediators of inflammation resulting from arachidonic acid. Their anti-inflammatory action also is produced on all tissue phases of the inflammatory process. They decrease vasodilation and vascular permeability, they slow chemotactility of neutrophils and reduce phagocytosis. Their immunosuppressant effect is manifest by damage to all cell lines that participate in immunity (inhi-

bition of T lymphocyte proliferation, inhibition of macrophage differentiation, decrease in number of circulating lymphocytes, neutrophils, eosinophils and basophiles, and mast cells, etc.) [28].

The intensity of action of glucocorticoids depends on their rate of absorption, their concentration in target tissues and their affinity for the receptor, their rate of biotransformation and clearance. The dose of a glucocorticoid defines the intensity of the therapeutic effects and the severity of the adverse events. These effects are proportional to the quantity of glucocorticoid saturated receptors [19]. In practice, different levels of doses are differentiated, defined for a reference subject (70 kg and 1.73m^2 body area) [19]:

- Low dose: if the dose is less than 7.5 mg prednisone-equivalent per day,
- Average dose: if the dose is between 7.5 mg and 30 mg prednisone-equivalent per day,
- High dose: if the dose is greater than 30 mg but less than 100 mg prednisone-equivalent per day,
- Very high dose: if the dose is greater than 100 mg but less than 250 mg prednisone equivalent per day,
- "Pulse" therapy if the dose is greater than 250 mg prednisone-equivalent per day.

In therapeutics, a glucocorticoid is chosen by looking for compounds which have a sufficient anti-inflammatory activity with adverse events which are inevitable but acceptable. Glucocorticoids with a mean duration of action of 12 to 36 are compounds that are the easiest to handle (prednisone, prednisolone, methylprednisolone) (Tab. 2 and 3).

1.4. Application of ice

Application of ice (cryotherapy) is a non-medical alternative or complementary method to the use of glucocorticoids to reduce the degree of oedema. In order to inhibit signs of inflammation and to obtain positive results by cryotherapy, skin temperature must be decreased by 10 to 15°C[61]. This temperature decrease is obtained after application of ice for about 10 minutes[46]. It produces local vasoconstriction, a

Table 2: Pharmacological properties of the principal glucocorticoids.

Trade name	Plasma half-life (min)	Mean duration of action (h)	Anti-inflammatory activity	Mineraloc orticoid activity	Dose equivalence (mg)
Cortisol	90	8-12	1	1	20
Cortisone	30	8-12	0.8	0.8	25
Prednisone	60	12-36	4	0.8	5
Prednisolone	200	12-36	4	0.8	5
Methylprednisolone	210	12-36	5	0	4
Betamethasone	270	36-54	25	0	0.75
Dexamethasone	270	36-54	25	0	0.75

Table 3: Trade names of glucocorticoids marketed in France.

INN	Trade name	Form	Dosage	Loading dose (oral route)
Betamethasone phosphate disodium	Betnesol®	Oral Parenteral	0.5 mg 4 mg/ml	0.05 to 0.2 mg/kg/day
Betamethasone	Celestene®	Oral	0.5 mg, 2 mg	0.05 to 0.2 mg/kg/day
Betamethasone acetate	Celestene Chronodose®	Intramuscular	5.7 mg/ml	1 injection during allergy period
Dexamethasone acetate	Dectancyl®	Oral	0.5 mg	0.05 to 0.2 mg/kg/day
Dexamethasone phosphate sodium	Dexamethasone Merck®	Parenteral	4 mg/ml	2 to 20 mg/day
Methylprednisolone acetate	Depo-Medrol®	Intramuscular	40 mg/ml	1 injection during allergy period
Methylprednisolone	Medrol®	Oral	4, 16, 32, 100 mg	0.3 to 1 mg/kg/day of methylprednisolone
Methylprednisolone succinate sodium	Methylprednisolone Dakotapharma®	Parenteral	10 mg/ml, 60 mg/ml	120 mg/day
Methylprednisolone	Methylprednisolone Merck®	Parenteral	20 mg, 40 mg, 500 mg, 1g	120 mg/day
Prednisolone acetate	Hydrocortancyl®	Local (injection)	125 mg/5ml	1/2 to 2 ml depending on site of injection and disorder to be treated
Prednisolone	Hydrocortancyl®	Oral	5 mg	0.35 to 1.2 mg/kg/day
Prednisolone metasulfobenzoate sodium	Solupred®, generic drugs	Oral	1 mg/ml, 5 mg, 20 mg	0.35 to 1.2 mg/kg/day
Prednisone	Cortancyl®	Oral	1, 5, 20 mg	0.35 to 1.2 mg/kg/day

reduction of oedema and decrease in pain perception. In the literature, only six clinical studies are found concerning application of ice in oral surgery [9,40,71,96,136,145]. Results of these studies are very different; only two [9,71] of them reported an improvement in post-operative symptoms with application of ice. None of them reported specific adverse events. However, cold urticaria is a contraindication to application of ice.

2. Indications of NSAIDs in oral surgery

Concerning indications for NSAIDs, the majority of studies sought to demonstrate their analgesic efficacy after oral surgical procedure. Very few of them investigated the anti-inflammatory activity (anti-oedema or decrease in trismus) of these substances.

2.1. Anti-inflammatory action

Bjørnsson et al. 2003 [16] showed that there was no significant difference between the intake of 2400 mg ibuprofen per day and 4000 mg paracetamol per day for 72 hours on oedema and opening of the mouth (level 2 of evidence).

Comparison between NSAIDs (flurbiprofen or ibuprofen) and glucocorticoids (prednisolone or methylprednisolone) showed that glucocorticoids significantly reduce more inflammatory symptoms (decrease in oedema and of trismus) than NSAIDs [123,131] (level 4 of evidence). On the contrary, NSAIDs systematically proved to be more effective than glucocorticoids to decrease pain.

No evidence exists to demonstrate that NSAIDs have superior efficacy on inflammatory events (œdema, trismus) than that of paracetamol or placebo (level 1 of evidence)

2.2. Analgesic action

All meta-analyses [Ahmad et al. 1997 [4] (level 1 of evidence 1); Sutherland et al. 2003 [127]

(level 2 of evidence);Romsing et al. 2004 [106] (level 2 of evidence)] confirm that the analgesic action of NSAIDs is superior to that of paracetamol or of placebo in postoperative pain in oral surgery. None of these meta-analyses make it possible to differentiate NSAIDs in terms of efficacy or safety. These studies confirm the analgesic efficacy of NSAIDs in oral surgery (level 1 of evidence) but they do not make it possible to arrange them into a hierarchy, nor to determine their relative efficacy or activity compared to the paracetamol-low potency opioid combination.

2.3. Modalities of use

2.3.1. Compounds

In oral surgery, all NSAIDs tested (ibuprofen, naproxen, flurbiprofen, ketoprofen, diclofenac, ketorolac, meclofenamate, etodolac, rofecoxib, etc.) are at least as effective as paracetamol [16,87], aspirin or low potency opioids on post-operative pain. The different studies did not make it possible to differentiate the efficacy of NSAIDs studied compared to each other [24,60,84,98,105,118,132,137,146] (level 2 of evidence). Ibuprofen is the NSAID which has been studied the most. A dose-effect relationship exists [115] (level 1 of evidence). In many studies, ibuprofen was prescribed at dosage greater than 1200 mg, a dose not authorised in France in the indication for analgesia [16,59,77]. The dose of 400 mg per dose seems to be the most effective analgesic dose in adults [15,31,57,85,115] (professional agreement). At the time of writing of these recommendations, the use of coxibs (anti-COX-2) was called into question. Some of them have been withdrawn from the market. Under these conditions and in the absence of an MA, their use in oral surgery is not recommended (professional agreement, HAS 2005) [53]. However, new compounds are under study, such as etoricoxib (Arcoxia®) which may obtain marketing authorisation in France for the indication for acute pain. In this case, it would be necessary to evaluate its utility in oral surgery

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2.3.2. Duration of treatment

Duration of treatment with an NSAID is based mainly on two factors:

– Duration of painful symptoms,

– Probability of occurrence of adverse events.

Since the duration of inflammatory and pain symptoms in oral surgery usually does not exceed 48 to 72 hours (HAS 2005) [53], analgesic treatment with an NSAID should not exceed 5 days (recommendation of SFAR) [124]. Duration of treatment in studies analysed is highly variable, ranging from a few hours to 7 days.

2.3.3. Route of administration

No difference exists in efficacy between oral, local, parenteral and rectal routes of administration (level 1 of evidence). Three randomised prospective studies have been identified [29,63,142]. They make it possible to conclude that there is no difference in efficacy depending on route of administration, either in situ or OD for ketoprofen gel, between IV injection or OD use for tenoxicam, and between OD and intra-rectal route for diclofenac. Similarly, Ong and Seymour 2003 [89] did not find any difference between the oral, parenteral and intra-rectal routes of administration (level 2 of evidence).

2.4. Contraindications

They are as follows:

– After 24 weeks of amenorrhea (over 5 months of pregnancy),

– Subjects over 65 years of age,

– History of allergy or asthma triggered by use of an NSAID or aspirin [73],

– An ongoing gastroduodenal ulcer or history o recent gastroduodenal ulcer (less than 6 months) or complicated ulcer,

– Chronic intestinal bowel disorders (IBD),

– Severe hepatocellular impairment,

– Severe renal impairment,

– Uncontrolled severe heart failure,

– NSAIDs are excreted in breast milk, and as a precautionary measure, they should not be administered to breastfeeding mothers.

Prescription of an NSAID is contraindicated in pregnant women starting from over 5 months of pregnancy. A true risk of serious foetal and/or neonatal toxicity exists after use of an NSAID by the mother in late pregnancy, foetal death in utero, neonatal death, renal and/or cardiopulmonary disorder. This risk exists even if prescription of an NSAID is of short duration (1 day), at usual dosage, in particular if it is administered just prior to delivery in non-obstetrical indications during normal, mono-foetal or full term pregnancy [34,58,101,129].

The damage described in the foetus and/or neonate exposed to NSAID in utero is subsequent to inhibition of foetal and neonatal prostaglandin synthesis. Such inhibition can cause vasoconstrictor effects on the following organs:

- the kidneys, resulting in foetal and/or neonatal transient or permanent renal impairment that can result in death,

- The cardiopulmonary system with constriction of the ductus arteriosus in utero that can cause:

  - Foetal death in utero,

  - Right heart failure and/or pulmonary arterial hypertension that is sometimes fatal in the neonate.

Without being an official contraindication, special precaution must be observed with use of an NSAID in pregnant women from the start of pregnancy. In fact, increasingly more miscarriages have been reported following use of an NSAID during the first months of pregnancy. Therefore, it seems reasonable to contraindicate prescription of these medicinal products throughout pregnancy.

2.5. Precautions for use

It is not advisable to prescribe an NSAID in a patient who presents with a risk of functional renal impairment (except in exceptional cases which then require laboratory test monitoring): elderly subjects (>65 years of age), hypovolaemia, treated with diuretic, angiotensin-converting enzyme inhibitor, or angiotensin 2 receptor antagonist.

The increased risk of adverse events must be taken into account in the elderly, in particular bleeding and/or potentially fatal gastrointestinal bleeding.

NSAIDs must be prescribed and used with caution in patients with a history of chronic inflammatory bowel disease (ulcerative

colitis, Crohn's disease) because there is a risk of exacerbation (30% of cases), or even of perforation.

NSAIDs are to be prohibited in patients with Fernand Widal syndrome or who have a history of atopy or asthma.

2.6. Adverse events

An analysis of the literature has not found any epidemiological studies or clinical trials dedicated to the study of adverse events of NSAIDs after an oral surgery procedure.

No prospective study concerning prescription of an NSAID in oral surgery has demonstrated serious adverse events with a causal relation to the NSAID. A multicentre, randomised, prospective study evaluated the risk of death, bleeding from the surgical site, gastrointestinal bleeding, acute renal failure and of allergic reaction after 7 days of treatment with ketorolac, diclofenac and ketoprofen [39]. This study involved 11,245 patients who underwent complicated surgery involving the oral cavity. Serious adverse events were observed in 155 (1.38%) patients: 19 (0.16%) deaths, 117 (1.04%) instances of bleeding from the surgical site, 12 (0.12%) allergic reactions, 10 (0.09%) instances of renal impairment and 4 (0.04%) instances of gastrointestinal bleeding (level 1 of evidence).

2.6.1. Post-operative bleeding
The risk of post-operative bleeding with a causal relation to use of an NSAID is poorly evaluated and data are contradictory. However, two meta-analyses have demonstrated that the NSAIDs increase risk of bleeding requiring repeat surgery after tonsillectomy by a factor ranging from 2 to 4 [74,81] (level 2 of evidence).

2.6.2. Infection
The cause-effect relationship between use of an NSAID and increase in risk of infection has not been clearly established. No study has demonstrated an increase in the incidence of

has demonstrated an increase in the incidence of infection after oral surgery, which was causally related to use of an NSAID. Moreover, a randomised placebo-controlled study that included almost 500 patients where NSAID were administered for short term therapy (48 hours) in patients with severe sepsis, showed that there was no increase in mortality nor increase in organ failure during treatment with an NSAID [13] (level 3 of evidence).

However, in the literature a few cases of infection have been found which seem to have been promoted by use of an NSAID [41,104,139]. (level 4 of evidence). In children with chicken pox and treated with NSAIDs, infectious complications of skin lesions (cutaneous abscess, cellulite, fasciitis, necrotising fasciitis, skin infection, skin necrosis, pyodermitis, gangrenous pyodermitis) sometimes serious have been observed. Such infectious complications appear exceptional and difficult to evaluate because chicken pox can lead to the same infectious complication of the skin and soft tissue in the absence of any treatment with an NSAID. The rare studies which have examined the favouring role of NSAIDs in these infectious complications do not make it possible to conclude. However, initiation of treatment with an NSAID for management of fever and/or pain is not recommended in children with chicken pox.

2.6.3. Gastro-intestinal disorders [6,8,12,55,67-69,99,103]
Gastro-intestinal disorders resulting from NSAIDs are among the most common adverse events. Generally they are non-serious (nausea, vomiting) and regress after discontinuation of treatment. However, NSAID can be responsible for serious gastro-intestinal adverse events (gastric and/or duodenal ulcer, GI perforation, GI bleeding, proctorrhagia, etc.). Different factors intervene to explain the incidence of these complications [1,54,66]:

- Age and gender and smoking: Risk increases significantly for men after age 55 years and for women after 65 years; men appear to be more affected than women by this complication, and smokers more than non-smokers.
- The dose used: The risk increases with the dose of NSAID used [53].

- Duration of treatment: This notion remains debateable, but however it appears that the risk is the same at the start of treatment as during long term treatment. For some authors, complications may develop starting from day 7 of prescription and become more common after day 50.
- Concomitant use of another NSAID – including low dose aspirin for anti-aggregant purpose – glucocorticoïds and anti-coagulants.
- History of gastrointestinal disorders: Ongoing gastroduodenal ulcer and chronic inflammatory bowel disease.

2.6.4. Renal complications [6,22,36,57,62,112,113]

The NSAIDs used in a short term course of therapy do not appear to produce a major increase in plasma creatinine. Similarly, the risk of renal impairment in a patient without a history of renal disorder is relatively low. However, this risk is greatly increased in the elderly and when NSAID are used in combination with diuretic agents or converting enzyme inhibitors [57] (level 2 of evidence).

2.6.5. Cardiovascular risk [6,12,14,22,32,36, 88, 112,113,122,135]

Factors responsible for cardiovascular risk related to use of NSAIDs, selective or not, have not been clearly identified. Based on recent randomised studies on conventional NSAID, there seems to exist an increase in arterial thrombotic risk. It may be lower for naproxen.
NSAID can also cause elevation of blood pressure or heart failure.

2.7. Drug interactions [3,12,100]

Drug interactions are observed with the following substances:
- Other non-steroidal anti-inflammatory agents
Combinations that are not advisable: enhancement of ulcer-causing risk and of GI bleeding.
- Acetylsalicylic acid
Combination not advisable with *acetylsalicylic acid at anti-inflammatory dose* (≥1g per dose and/or ≥ 3g per day) at

analgesic or antipyretic dosages (≥ 500 mg per dose and/or < 3 g per day).
Contraindication to be taken into account with acetylsalicylic acid at anti-agreggant doses (from 50 mg to 375 mg a day in 1 or more doses). Enhancement of the ulcer-inducing and GI bleeding risk.
- Angiotensin II receptor antagonists
Precautions for use: Sufficient fluid intake should be given to the patient. Monitor renal function at start of treatment. Acute renal failure in patients at risk (elderly and/or dehydrated subjects) due to a decrease in glomerular filtration (inhibition by vasodilator prostaglandins caused by non-steroidal anti-inflammatory agents). Moreover, reduction of the anti-hypertensive effect.
- Oral anti-coagulants
Combinations that are not advisable: with other NSAIDs. If such a combination cannot be avoided, clinical and close laboratory monitoring is necessary.
Increase in bleeding risk with oral anti-coagulant (aggressive action on the gastroduodenal mucosa by non-steroidal anti-inflammatory agents).
- Beta-blockers (except esmolol)
To be taken into account: Reduction of the anti-hypertensive effect (inhibition of vasodilator prostaglandins by non-steroidal anti-inflammatory agents and salt and water retention with pyrazole non-steroidal anti-inflammatory agent).
- Cyclosporine: Risk of additive nephrotoxic effects, in particular in the elderly.
Precautions for use: Monitor renal function at start of treatment with an NSAID.
- Diuretics
Precautions for use: Administer sufficient fluid intake to the patient and monitor renal function at start of treatment. Acute renal failure in at risk patients (elderly and/or dehydrated patient) due to a decrease in glomerular filtration (inhibition of vasodilated prostaglandins due to non-steroidal anti-inflammatory agents). Furthermore, reduction of the antihypertensive effect.
- Glucocorticoids (except hydrocortisone in replacement therapy)
To be taken into account: Increase in risk of ulceration and gastrointestinal bleeding

- Low molecular weight heparins and related compounds (at curative dosage and/or in the elderly)

Combinations that are not advisable: If such a combination cannot be avoided, close clinical monitoring is necessary. Increase in risk of bleeding (aggressive action on the gastrointestinal mucosa by non-steroidal anti-inflammatory agent gastroduodenal mucosa)

- Low molecular weight heparins and related (preventive dosage)

To be taken into account: Increase in risk of bleeding

- Unfractionated heparins (UFH) (at curative dosage and/or in the elderly)

Combinations that are not advisable: If such a combination cannot be avoided, close clinical monitoring is necessary.

An increase in the risk of bleeding (aggressive actions on the gastroduodenal mucosa by non-steroidal anti-inflammatory agents.

- Unfractionated heparin (at preventive doses)

To be taken into account: Increase in risk of bleeding

- Angiotensin-converting enzyme (ACE) inhibitors

Precautions for use: Administer sufficient fluid intake into the patient and monitor renal function at start of treatment. Acute renal failure in at risk patients (the elderly and/or dehydrated subjects) due to a decrease in glomerular filtration (inhibition of vasodilator prostaglandins caused by non-steroidal anti-inflammatory agents).

Furthermore, reduction of the anti-hypertensive effect.

- Selective serotonin reuptake inhibitors

To be taken into account: Enhancement of risk of bleeding.

- Lithium: Increase in serum lithium that can reach toxic levels (decrease in renal excretion of lithium).

Combinations that are not advisable: If a combination cannot be avoided, monitor serum lithium closely and adjust dosage of lithium during combination and after discontinuation of non-steroidal anti-inflammatory agent

- Methotrexate: Increase in haematological toxicity of methotrexate (decrease in renal clearance of methotrexate by anti-inflammatory agents)

Combinations that are not advisable: With other non-steroidal anti-inflammatory agents and doses of methotrexate greater than 20 mg per week. With ketoprofen and methotrexate at doses greater than 20 mg per week, an interval of at least 12 hours must be complied with between the end or start of treatment with ketoprofen and use of methotrexate.

Combination requiring precautions for use: With other NSAIDs and methotrexate used at low dose (doses less than or equal to 20 mg per week), weekly measurement of CBC during the first weeks of the combination use. Increased monitoring in the event of a deterioration (even slight) in renal function as well as in the elderly.

- Pemetrexed: Risk of worsening of toxicity of pemetrexed (decrease of its renal clearance by an NSAID)

Combinations not advisable: In patients with low to moderate renal function (creatinine clearance between 45 ml/min and 80 ml/min).

Precaution for use: In patients with normal renal function. Laboratory monitoring of renal function.

- Tacrolimus: Additive risk of nephrotoxic effects, in particular in the elderly.

Precautions for use: Monitor renal function at start of treatment with an NSAID.

2.8. Choice of an NSAID

The choice of an NSAID must be made by taking into account its profile of safety for use (based on the summary of product characteristics) and on a patient's individual risk factors.

Replacement of one NSAID by another must not be done without taking into consideration these two items.

In choosing an NSAID, it is necessary:

- To comply with its indications and dosage.

NSAIDs must always be prescribed and used:

– at the minimal effective dose,

– for the shortest possible duration (3 days, maximum 5 days).

Continuation of treatment with an NSAID, including with a coxib, is not justified outside of symptomatic manifestations of osteoarthritis or rheumatoid arthritis.

- Comply with contraindications,

- Comply with precautions for use,
- Take into account risk of drug interactions.

3. Indications for glucocorticoids in oral surgery

The use of glucocorticoids in oral surgery was introduced in the 1950s [125]. It aims mainly to obtain a reduction of the manifestations of the physiological inflammatory process.

All studies found in the literature reveal a very wide heterogeneity in modalities for use of glucocorticoids, and this is true both in terms of compound, dosage, routes of administration (OD, parenteral route) and modalities for administration (single dose, repeated dose). The glucocorticoids most commonly found in the literature are prednisone, methylprednisolone and dexamethasone [5]. Clinical studies week primarily to study the efficacy of glucocorticoids on post-operative follow-up after extraction of wisdom teeth. They are evaluated based on their analgesic anti-oedema properties and their ability to reduce trismus.

3.1. Analgesic activity

Concerning evaluation of the analgesic activity of glucocorticoids, the following studies have been found in the literature.

Sisk et al. (1985) [123]: 18 patients received an IV injection of 125 mg methylprednisolone just prior to procedure. Pain was evaluated by means of a visual analogue scale (VAS) and a simple numerical scale (SNS - 4 points) for the first 8 hours, and then via SNS only for 7 days. No superior effect of methylprednisolone was found between time 2 and 6 hours compared to placebo. At a time of 7 hours, pain was significantly lower. No superior analgesic effect was found starting from time 24 hours (level of evidence 2). Neupert et al. (1992) [83]: 60 patients received 4 mg of dexamethasone by IV injection 5 to 10 minutes before the procedure. There was no significant difference for pain compared to placebo (level of evidence 4).

Schultze-Mosgau et al. (1995) [116]: Patients received 32 mg of methylprednisolone 12 hours before the procedure and 12 hours after, in combination with 400 mg ibuprofen every 5 hours on day of procedure and the two following days. Pain was evaluated by a VAS and SNS one hour after each dose of analgesia. A reduction in pain of 67.7 % then was observed compared to placebo (level of evidence 4).

Troullos et al. (1990) [131]: This article actually contains two studies. In the first one, the dose of 100 mg flurbiprofen 30 minutes before the procedure was compared versus one injection 125 mg methylprednisolone at the start of the procedure and versus a placebo. In the second study, the first group of patients received 600 mg ibuprofen before the procedure and then 600 mg every 6 hours for two days. The second group received 125 mg methylprednisolone before the procedure and then 10 mg oxycodone every 6 hours. The third group received a placebo. Results showed better post-operative analgesia in the NSAID groups during the first 3 post-operative hours (level of evidence 4).

Dione et al. (2003) [30]: In this study, a first group received 400 mg OD of dexamethasone 12 hours before the procedure, 4 mg of dexamethasone by IV injection one hour before the procedure, and then a placebo by IV injection at time of occurrence of pain. The control group received the same treatment but at time of occurrence of pain, an IV injection of 30 mg ketorolac was administered. Pain was significantly decreased in the group treated with glucocorticoids and ketorolac compared to the group treated with glucocorticoids alone (level of evidence 4).

Esen et al. (1999) [33]: In this cross-over placebo-controlled study, treatment with 125 mg methylprednisolone by IV injection resulted in a significant decrease of pain in the treated group at D0 only (level of evidence 1).

In all these studies, the analgesic activity of the glucocorticoid proved to be modest and was always less than that of the NSAID (level of evidence 1).

This had already been reported in recommendations of HAS (2005) in the "Prevention and treatment of post-operative pain in oral surgery" [53].

3.2. Anti-oedema activity

Pedersen (1985) [92]: An IM injection of 4 mg dexamethasone immediately pre-operatively reduce oedema by 50% at D2 versus placebo, but there was no difference at D7 (level of evidence 2).

Milles and Desjardins (1993) [79]: With 16 mg methylprednisolone OD the night before the procedure, and then 20 mg methylprednisolone by IV injection pre-operatively, a 42% reduction was obtained in oedema at D1 and then 34% at D2 compared to placebo (level of evidence 4).

Schaberg et al. (1984) [110]: With 1 mg/kg methylprednisolone by pre-operative IV injection for an orthognathic surgery procedure, a 62% reduction on oedema was observed at D1 (level of evidence 4).

Neupert et al. (1992) [83]: 4 mg dexamethasone in an IV injection pre-operatively did not produce any decrease in oedema (level of evidence 4).

Esen et al. (1999) [33]: In this prospective, randomised, double-blind, intra-patient study, treatment with 125 mg methylprednisolone by pre-operative IV injection made it possible to obtain a 42% reduction on oedema at D2 compared to placebo (level of evidence 1).

Ustun et al. (2003) [134]: In this prospective, randomised, double-blind, intra-patient study there was no significant difference between 1.5 mg/kg and 3 mg/kg methylprednisolone by IV injection pre-operatively on oedema at D2 (level of evidence 2).

Finally, in all the studies, when the dose of glucocorticoids was sufficient (greater than 50 mg prednisone equivalent), a decrease in post-operative oedema was observed. This decrease was significant between D2 and D3 but no longer was so at D7, whatever the glucocorticoid and dose used. This justifies that the prescription must not exceed 72 hours.

3.3. Decrease of trismus

Milles et al. (1993) [79] showed a reduction of oedema with no significant difference for trismus (16 mg methylprednisolone OD 12 h prior to the procedure + 20 mg by IV injection just before the procedure). Similarly, methylprednisolone (125 mg IV injection pre-operatively) did not appear sufficient to reduce trismus [11,123] even though it decreased oedema. On the contrary, 40 of by IM injection enabled a reduction of trismus at D2 [78].

Conversely, Neupert et al. (1992) [83] observed a decrease in trismus with 4 mg dexamethasone by IV injection even though this dose is insufficient to obtain an anti-oedema action; the same result was obtained for Pedersen (1985) [92] with 4 mg dexamethasone by IM injection. The use of dexamethasone (6 mg OD 12 hours before and after procedure) enabled a reduction of trismus and of oedema at D1 [114].

The results obtained in decrease of trismus after an oral surgery procedure are very different. Depending on studies for a given dose of glucocorticoids and the same route of administration, results are contradictory and often there is no significant difference between the treated patients and those who received placebo (level of evidence 1).

3.4. Modalities for use

3.4.1. Choice of a glucocorticoid

The most commonly used glucocorticoids in studies concerning oral surgery are dexamethasone and methylprednisolone in all forms (OD, parenteral) (Tab. 2). No data from the literature makes it possible to choose one glucocorticoid instead of another. Dexamethasone is the glucocorticoid most widely studied [5]. Wide pharmacokinetic differences exist between the different glucocorticoids. The bioavailability of prednisolone is higher after biotransformation of prednisone than after that of prednisolone metasulphobenzoate. This appears to be correlated with a greater clinical efficacy for prednisone, which should be preferred for treatments by systemic route [128]. In practice, this observation is important for long term steroid therapy, probably much less so for short courses of therapy.

3.4.2. Choice of dose

In the literature, the dose prescribed is highly variable, ranging from a mean dose (25 mg prednisone equivalent [21]) to very high doses (156 mg prednisone-equivalent [11]). Doses less than 50 mg prednisone-equivalent [43] appear to be ineffective on clinical signs of inflammation. Others [43] propose administration of a dose of glucocorticoids greater than 300 mg cortisol (75 mg prednisone-equivalent), the dose produced physiologically in a situation of stress. For oedema and trismus, efficacy appears dose-dependent. Doses between 50 mg prednisone equivalent and 156 mg prednisone equivalent appear to be effective and did not present any adverse events reported in the literature. The mean

daily dose recommended is 1 mg prednisone equivalent per kg body weight (professional agreement).

3.4.3. Choice of route of administration

Glucocorticoids can be administered by mouth or by parenteral route (IM or IV injection).

3.4.3.1. Oral route

Administration of 8 mg dexamethasone, 2 hours before the procedure, produces pain and less oedema at time 4 hours than in the placebo group. Opening of the mouth was identical in the two groups [10]. Schmelzeisen and Frölich (1993) [114] in a double-blind cross over study demonstrated that at a dose of 6 mg dexamethasone 12 hours before and after a procedure significantly reduces pain, oedema and post-operative trismus at D1 but that there was no significant difference between the two groups for the three criteria at D3 and D7.

A dose of 84 mg methylprednisolone for 4 days significantly decreased oedema and trismus at D3 but did not alter the pain scores [86].

Alexander and Throndson (2000) [5] proposed 8 mg dexamethasone the evening before the procedure, a loading dose of 12 to 16 mg before the procedure, and the same dose at D1 and D2.

None of these studies made it possible to recommend one compound or one dose of

glucocorticoid by oral route. Administration of a glucocorticoid by oral route enables complete and rapid absorption. However, this route requires repeated administration in a manner to maintain sufficient plasma concentration. Treatment generally must have been started two to four hours before the procedure to obtain the best efficacy.

3.4.3.2. Intramuscular route

Use of 4 mg dexamethasone pre-operatively revealed an anti-oedema effect and reduction of trismus at D2 and D7 [92].

The intramuscular route was evaluated for prednisolone at a dose of 25 mg in immediate post-operative [21]. Anti-inflammatory activity activity appeared effective at D2 and D7.

Injection of 40 mg The injection of 40 mg methylprednisolone post-operatively appeared to show efficacy at D2 [78].

Injection of 40 mg methylprednisolone in the masseter post-operatively may produce a favourable effect on trismus, pain and oedema [140].

3.4.3.3. Intravenous route

The injection of 125 mg prednisolone pre-operatively produced a decrease in oedema at D1 and D2 [131].

Injection of 125 mg methylprednisolone by IV route may have an action on oedema but not action on trismus [11,123]; other authors [33] obtained different results. Moreover, Ustun et al. [134] did not find a different anti-inflammatory effect between IV injection of 1.5 mg/kg or 3 mg/kg. 4 mg dexamethasone made it possible to reduce trismus but had no action on oedema [83].

In summary, data from the literature do not make it possible to prefer one route of administration more than another. Outside of the hospital setting, the oral route is recommended because of its ease of execution and its safety (professional agreement).

3.4.4. Rate of administration

To be effective, glucocorticoids must be administered before the surgical procedure, whatever the route of administration chosen and not during or after the procedure [7,114].

3.4.4.1. Oral route

Oral forms must be administered at least 2 to 4 hours before the procedure in order to obtain sufficient tissue concentrations. In the selected studies, the administration of glucocorticoids was given 12 hours before and 12 hours after the procedure [29,114,116], 2 hours before the procedure [86,87] or 2 hours after the procedure [86].

3.4.4.2. Intramuscular route

Intramuscular administration is performed either pre-operatively [92] or immediately post-operatively [21,78,140].

3.4.4.3. Intravenous route

Intravenous administration is performed pre-operatively [12,33,79,83,123,131,134]. The IV route has immediate clinical utility on pain, oedema and trismus but requires re-administration of glucocorticoids by IM route or OD subsequently.

In summary, there is no sufficient amount of data in the literature to determine the rate of administration of glucocorticoids in oral surgery, whatever the route of administration used. The adverse events, such as neuropsychological disorders (euphoria, insomnia, excitation), frequently encountered with use of glucocorticoid should lead to an administration in a single dose in the morning [25] (professional agreement).

Duration of inflammatory symptoms (oedema, trismus) does not require use of glucocorticoids for more than three days. This involves a short course of therapy, which enables the sudden discontinuation of treatment.

3.5. Adverse events

Glucocorticoids are known for their adverse events directly related to their pharmacological properties. The importance and frequency of adverse events depends on duration of treatment and the dose used Moreover, a wide inter-individual variability exists [111,141].

An analysis of the literature did not make it possible to find clinical studies which in particular involved adverse events related to use of glucocorticoids for

an oral surgery procedure. No serious adverse event was reported. Only non-serious adverse events not requiring specific treatment have been reported and most often they were not attributable to the glucocorticoids themselves.

3.5.1. Inhibition of the hypothalamus-pituitary-adrenal axis

Only one study examined the effect of use of glucocorticoids on the hypothalamic-pituitary-adrenal gland axis [18]. It showed a major decrease in levels of cortisol at D3 (a 50% reduction of normal levels), followed by a return to normal at D7. In practice, this inhibition has no clinical impact, which authorises the sudden discontinuation of treatment without progressive tapering of the dose [50]. In addition, in the absence of a clinical impact, it is not necessary that doses be administered strictly at 8 o'clock in the morning (professional agreement).

3.5.2. Infection

Inhibition of the immune system and of the inflammatory process represents two central components of the action of glucocorticoids. The result is an increase in risk of infection during steroid therapy. Furthermore, its anti-inflammatory action partly masks the signs of infection, which can delay the diagnosis.

In a retrospective study, analysing 71 clinical studies, Stuck et al. (1989) [126] evaluated the increase in relative risk as 1.6 in patients who were under long term steroid therapy. The rate of infection was not increased for patients who received a dose less than 10 mg prednisone equivalent. Although this risk is not strongly increased by moderate doses of glucocorticoids, opportunistic infection and infectious complications nevertheless appeared to be more frequent outside of short courses of therapy, apart from in subjects with immunocompromised status. An increase in the incidence of active tuberculosis, in oral candidiasis and complications related to chicken pox has been described [111]. Cases of malignant anguillulosis during steroid therapy have been reported [128].

In the studies classified, some have been conducted without antibiotic prophylaxis. No mention was made of an increase in the incidence of risk of infection. These studies were as follows: Schultze-Mosgau et al. (1995) [116]: with 32 mg methylprednisolone 12 h before and 12 h after the procedure, in combination with 400 mg ibuprofen 3 times daily for 3 days, two patients developed a wound infection, 1 patient (8%) in the placebo group and 1 patient (8%) in the active treatment group.

Milles and Desjardins (1993) [79]: with 16 mg methylprednisolone OD 12 hours before a procedure and 20 mg methylprednisolone by IV injection immediately pre-operatively. There was no adverse event attributable to glucocorticoids in the study on 11 patients. Neupert et al. (1992) [83]: a study on 60 patients, the treated group received 4 mg dexamethasone by IV injection 5 to10 minutes pre-operatively. There was no increase in the incidence of adverse events in the treated group: 4 patients (2 in each group) (3%) presented with a minor infection, 9 patients (15%) had alveolitis 4 of whom in the glucocorticoid group.

Troullos et al. (1990) [131]: In a study on 98 patients with 125 mg methylprednisolone by IV injection at start of the procedure, the adverse events observed (drowsiness, dizziness, agitation, malaise, nausea and vomiting) were divided in the three groups (NSAID, methylprednisolone and placebo); they were probably partly due to the systematic prescription of diazepam by IV injection. There was a statistically significant decrease in cortisol levels 24 and 48 hours after the injection of methylprednisolone or use of an NSAID (flurbiprofen 100 mg or ibuprofen 600 mg 30 minutes before the procedure). There was no difference in incidence of infections in the three groups; but its evaluation requires a larger cohort. Sisk and Bonnington (1985) [123]: In 18 patients who received 125 mg methylprednisolone by IV injection at start of the procedure, the following adverse events were observed: drowsiness (44.4%), effects on the central nervous system (27.7%), and gastrointestinal disorders (5.5%).

After an oral surgery procedure, no item makes it possible to conclude in an increase in the incidence of post-operative infection which is attributable to glucocorticoids. Glucocorticoids in a short course of therapy do not appear to promote infection.

Therefore, it is not necessary to initiate antibiotic prophylaxis for the sole reason that the patient is receiving glucocorticoids in the short term course of therapy. Antibiotic therapy and antibiotic prophylaxis retain their specific indications (Recommendations of AFSSAPS, 2001) [2] independently of prescription of glucocorticoids (professional agreement).

3.6. Precautions for use

In the event of gastro-duodenal ulcer, steroid therapy is not contraindicated if an anti-ulcer treatment is given concomitantly. In patients with a history of ulcer, steroid therapy can be prescribed under close clinical monitoring and, if necessary, after OEGD.

Steroid therapy sometimes promotes the occurrence of infectious complications, in particular due to bacteria, yeasts and parasites (malignant anguillulosis etc.).

Progressive signs of infection can be masked by steroid therapy. Before initiation of treatment, it is necessary to rule out all possible internal organ focus of infection, in particular with tuberculosis and during treatment to monitor the patient for occurrence of any infectious disease. Use of glucocorticoids requires especially adapted monitoring, in particular in the elderly, in presence of ulcerative colitis or diverticulosis (risk of perforation), of recent intestinal anastomosis (< 1 month ago), of renal or hepatic impairment, of osteoporosis or off myasthenia gravis. Data from the literature did not make it possible to define the approach to be taken for patients following long term glucocorticoid therapy. Possible increase in dosage must be discussed with the prescribing doctor.

3.7. Contraindications

Contraindications to use of glucocorticoids in oral surgery are as follows:

- Known hypersensitivity to one of the components,
- Any infection, to the exclusion of specific indications (septic shock, bacterial meningitis, etc.),
- Certain progressive viral diseases (in particular hepatitis, herpes, chicken pox, herpes zoster),
- Psychotic conditions not controlled by treatment,
- Live vaccines

3.8. Drug-drug interactions

Many drug interactions exist [3].

3.8.1. Combinations that are not advisable
- Sultopride: It involves an enhanced risk of ventricular arrhythmia, in particular torsades de pointes; hypokalaemia is a promoting factor.
- Other medicinal products which cause torsades de pointes are not formally not advisable (see following paragraph).

3.8.2. Combinations requiring precautions for use
- Acetylsalicylic acid by systemic route (aspirin) and, by extrapolation, other salicylates: A decrease in serum salicylic acid levels during treatment with glucocorticoids (increase in elimination of salicylates by glucocorticoids), and risk of a salicylate overdose after its discontinuation and thus the need to adjust doses of salicylates during combination and after the end of treatment with glucocorticoids.
- Oral anti-coagulants: Possible impact of steroid therapy on metabolism of an oral anti-coagulant and on coagulation factors. Furthermore, high dose steroid therapy or in extended treatment greater than 10 days involves a specific risk of bleeding (GI mucosa, vascular frailness). When such a combination use is justified, monitoring must be enhanced: laboratory test

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measurement at day 8, and then every 2 weeks during steroid therapy and after its discontinuation. Other potassium-lowering agents: With potassium lowering diuretics alone or in combination, with stimulant laxatives, amphotericin B (IV route), tetracosactide, an enhanced risk of hypokalaemia exists due to the additive effect. Monitoring of serum potassium

account in particular in the event of treatment with digitalis. Use non-stimulant laxatives.
- Cardiac glycosides (digitalis): Hypokalaemia promotes the toxic effects of cardiac glycosides and thus the need to monitor serum potassium and, if necessary, to record an ECG.
- Heparins by parenteral route: Heparin worsens the risk of bleeding specific for steroid therapy (GI mucosa, vascular fragility) at high doses or in extended treatment greater than 10 days. The combination must be justified and monitoring must be reinforced.
- Enzyme-inducing agents: With anti-convulsants (carbamazepine, phenobarbital, phenytoin, primidone), rifabutin and rifampicin, there is a decrease in plasma concentrations and of efficacy of glucocorticoids by an increase in their metabolism in the liver. The effects are especially important in patients with Addison's disease and in the event of transplantation. Clinical and laboratory monitoring must be performed and dosage adjustment of glucocorticoids during combination use and after the end of use of an enzyme-inducing agent.
- Insulin, metformin, hypoglycaemic sulphonylurea compounds, repaglinide and, by extrapolation, tetracosactide: Elevation of blood glucose sometimes causes ketosis (a decrease in tolerance to carbohydrates by glucocorticoids). The patient must be asked to reinforce his or her self-monitoring of blood and urine levels, in particular at start of treatment, which possibly leads to adjust dosage of the anti-diabetic agent during treatment with a glucocorticoid and after its discontinuation.
- Isoniazid (described for prednisolone): A decrease in plasma concentrations of isoniazid is observed, probably by an increase in metabolism of isoniazid in the liver and a decrease in that of glucocorticoids. Clinical and laboratory test monitoring is needed

Medicinal products which cause torsades de pointes (except sultopride): class Ia anti-arrhythmia agents (quinidine, hydroquinidine, disopyramide); class III anti-arrhythmia agents (amiodarone, dofetilide, ibutilide, sotalol); certain neuroleptic agents: phenothiazine-like compounds (chlorpromazine, cyamemazine, levomepromazine, thioridazine), benzamides

(amisulpride, sulpiride, tiapride), butyrophenones (haloperidol, droperidol), other neuroleptic agents (pimozide); other agents: bepridil, cisapride, diphemanil, erythromycin by IV injection, halofantrine, mizolastine, moxifloxacin, pentamidine, spiramycin by IV injection, vincamine by IV injection: enhanced risk of ventricular arrhythmia, in particular of torsades de pointes (hypokalaemia is a promoting factor). All hypokalaemia must be corrected before administering the product, and clinical, electrolyte and electrocardiographic monitoring must be performed.

- Gastro-intestinal topical agents (described for prednisolone and dexamethasone): They result in decreased GI absorption of glucocorticoids. The patient should be advised to take a gastrointestinal topical agent at an interval from a glucocorticoid (more than 2 hours apart of possible).

3.8.3. Combinations to be taken into account

- With anti-hypertensive agents (except beta-blockers): Decrease in the anti-hypertensive effect (salt and water retention of glucocorticoids).
- Interferon alpha: Risk of inhibition of action of interferon.
- Attenuated live vaccines and, by extrapolation, tetracosactide: Risk of a generalised disorder possibly fatal. This risk is enhanced in patients with immunocompromised status with an underlying disease. In particular, use an inactivated vaccine when it exists (poliomyelitis).

Data from the literature concerning indications for glucocorticoids are summarised in table 4; in the absence of data, the working group issued an opinion.

Table 4: Indications for glucocorticoids in oral surgery for each procedure.

Procedure	R: recommended / NR: not recommended	References
Tooth extraction		
- Healthy tooth	NR	
- Separation of dental roots	NR	
- Alveolectomy	NR	
- Removal of a dental root	NR	
- Wisdom teeth	R	
- Impacted tooth or disimpaction	R ?	21, 45, 49, 78, 90, 130
- Germectomy	R	
Periapical surgery	NR	23, 66, 93
Depending on size of lesion and duration of procedure	NR/R	93
Transplantation/re-implantation	Depending on tooth and type of impaction	
Periodontal surgery	NR	
Unbound gingival transplantation	R	47
Connective tissue transplantation	NR	52
Unit implant surgery	NR	44
Multiple implant surgery, guided bone regeneration	R	44
Set up of filling materials		
Depending on extent and location of filling	NR?	
Bone graft (onlay) Depending on extent of bony defect and its localisation of the donor and recipient sites	R?	
Filling of a sinus	R?	
Pre-orthodontic surgery of impacted or embedded teeth	NR?	
Soft tissue surgery (biopsy of the mucosa, or of the accessory salivary glands)	NR	
	R	
Nerve trauma	R	119
Frenectomy		

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Note from the working *group*: After writing the final version of thes recommendations, the following article was published:

Markiewicz MR, Brady MF, Ding EL, Dodson TB. Corticosteroids reduce postoperative morbidity after third molar surgery: a systematic review and meta-analysis. J Oral Maxillofac Surg 2008; 66: 1881-94.

In this article the authors made a review of the literature and a meta-analysis on the prescription of glucocorticoïds in oral surgery; they came to the same conclusions as those of the working group.