• Local anesthesia in odontostomatology is a very frequent procedure in daily practice. The material used is standardized and includes “anesthetic cartridges” in glass, and special syringes called “with cartridge”. Each “cartridge” contains an injectable solution of amide type local anesthetic, like lidocaine.

• For many years, it has been customary practice to associate a vasoconstrictor (in general, adrenaline or noradrenaline) with the anesthetic solution.

• Few tests compared local dental anesthesia with vasoconstrictor versus no vasoconstrictor. The vasoconstrictor seems to improve the effectiveness and the duration of the anesthesia.

• Anesthetic associations containing 1/200,000 adrenaline concentration seem to present the most favourable balance benefit-risks. At this concentration, the quantities of adrenaline injected during everyday dental care remain minimal.
• During a local anesthesia for dental care by adrenaline solution, the serious undesirable events are rare estimated at 0.07 % in a German study, and they do not seem related to the presence of the vasoconstrictor.

• With the used quantities in the regular care, the only adverse effects related to the presence of adrenaline are an increased duration of the bleeding after dental extraction (low level of evidence), a tachycardia, and a light increase in the blood pressure without clinical consequence observed.

• In the absence of a specific study, for the diabetic, adding adrenaline in the dental anesthesia does not seem to have a harmful effect.

• We have observed use with a few dozen patients having cardiac pathology. No serious adverse effect was noted.

• In practice, the addition of adrenaline to the local anesthetic does not increase the risks of adverse effects, for the quantities regularly used: there is no contra-indication due to adrenaline.
Increasing patients’ request for dental care without pain has made local anesthesia very frequent in today’s odontostomatology practice (read in the framed box on pages 374-375).

Currently, in France, we have several local anesthetics for dental use. These anesthetic substances are all amide type, like lidocaine (aka lignocaine). Systemic adverse effects of these local anesthetics are rare. They occur especially in case of vascular injection or high treatment dosage: In question are neurological excitation type reactions, up to convulsions, and vasodilatation type cardiovascular reactions, hypotension and bradycardia, which can cause a heart failure (1). The allergic accidents are rarer in the amide type local anesthetics reported to ester type, such as procaine formerly used (a,b).

The preservative agent is sometimes highlighted the potential benefit of the association between a vasoconstrictor and a local anesthetic solution, to administer by intramuscular or epidural way for example (2).

In these studies, the association of a vasoconstrictor traduced in the reduction of the systemic diffusion of the anesthetic substance (reduction of the plasmatic concentration peak), by the increase in effectiveness of the local anesthesia (in duration, speed of anaesthetizing effect, and necessary quantity), and in the reduction of the local bleeding during a surgical procedure (2).

**Very few quality clinical studies in odontostomatology.**

To our knowledge, there are very few studies evaluating the clinical interest to associate a vasoconstrictor with a local anesthetic (3,4). Since the 1970s, the majority of tests evaluating the effectiveness of dental use anesthetics were led to solutions containing a vasoconstrictor, especially adrenaline (5 to 9). In 1991, a randomized clinical trial, non-blind, among 544 patients, compared the effectiveness of an anesthetic solution of articaine with vasoconstrictor (adrenaline at 1/200,000), versus a solution of articaine without vasoconstrictor, for various acts of dental surgery (3). Anesthesia failures were more frequent and the average anesthesia duration was less long in the group without vasoconstrictor: respectively, 7 % failure and 32.7 minutes without adrenaline, versus less than 1 % and 43.2 minutes with adrenaline (3).

A less methodological quality test had in the same sense going results (4).

**Choice of the adrenaline concentration: little assessment**

In dental field, the quantity of adrenaline contained in a cartridge of anesthetic varies according to the areas. In France like in Great Britain, the majority of the adrenaline anesthetic solutions contain 9 µg or 18 µl adrenaline per 1.8 ml cartridge, or a concentration from 1/200,000 to 1/100,000 (lo,11,12).

There are a very small number of clinical studies evaluating the optimal concentration of adrenaline in anesthetic solutions for dental use. The majority of the studies available date from the 1960’s, and were performed with lidocaine. These studies showed a similar effectiveness in terms of duration, depth of anesthesia and reduction of the bleeding for concentrations of adrenaline from 1/300,000 to 1/50,000 (2,13).

More recently, the comparative clinical trials evaluating the effectiveness of different anesthetics for dental use, used a concentration of adrenaline varying from 1/100,000 to 1/200,000 (9,14). All things considered, the expected benefits of adding adrenaline to the local anesthetic does not justify the use of adrenaline concentrations higher than the weakest available concentrations, namely 1/200,000 (11,12,13).

**Adverse effects associated with vasoconstrictors are very rare.**

Adverse effects from dental care under local anesthesia can be associated with the anesthetic, the vasoconstrictor or the care. In most studies, it is not possible to distinguish the real cause of the observed disorders.

A rigorous test does not exist, showing that the addition of a vasoconstrictor increases the risk of adverse effects, nor that it decreases the risks associated with the anesthetic. Serious adverse effects are atypical. There is not much epidemiologic data concerning serious adverse effects of local anesthetics in odontostomatology.

In Great Britain, between 1970 and 1979, local anesthesia during dental care was a factor in at least 6 deaths (15).

Some cases of methemoglobinemia after use of various local anesthetics were reported (ref 3).

According to a reference work in clinical pharmacology, in a single dose for local anesthesia, the maximum recommended treatment dosage of non-associated lidocaine is 200 mg in the United Kingdom (either the equivalent of approximately 3 cartridges of 2 ml of lidocaine at 2 %) and 200 mg in the United States of America (ref. 34).
In only one case, adrenaline was associated with the local anesthetic, 3 other deaths seem due to local anesthetic + noradrenaline associations (15).

These deaths occurred by cerebral hemorrhage probably related to a hypertensive shock (15). After several decades, serious hypertensive shocks have been described with noradrenaline at strong concentration (1/25,000) (c)(15,16). According to certain authors, solutions with strong proportions in noradrenaline should not be used any more (15,16).

The incidence of deaths notified following a local anesthesia however remains extremely weak, considering the 70 million cartridges used on average each year, during this period in Great Britain (15).

Concerning France, we did not find such data on drug monitoring, or in published death cases following a local anesthesia in odontostomatology, although the obligation to notify about the serious adverse effects is also mandatory for dental-surgeons (d).

Sometimes benign and transitory general adverse effects. In 1997, a study conducted in Germany tried to evaluate the incidence of the adverse effects among 2 731 patients involved in a local anesthesia during dental care (e) (17). For almost all of the patients, the associated local anesthetic was adrenaline.

In this study, the global incidence of the adverse events amounted to 4.5 %, without being able to distinguish the events related to the substances injected from the events associated with the apprehension of the gesture (17). The adverse events observed (vertigo, tachycardia, agitation, nausea, tremors) were for the most part transients, not requiring treatment. 12 vagal attacks were reported. 2 severe complications occurred (a convulsive crisis and a bronchospasm), that means an incidence of 0.07 %.

More recently, a randomized double blind test, jointly performed in the United States of America and in Great Britain, evaluated the effectiveness and the adverse effects of an anesthetic solution of articaine 4% versus those of a solution of lidocaine 2% (both with adrenaline at 1/100,000) for oral surgery procedures (14).

In total, 882 patients in the articaine group and 443 in the lidocaine group took part in this study. No serious complications were reported.

22% of the patients of the articaine group reported at least one undesirable event, versus 20% in the lidocaine group (no statistically significant difference). The adverse events were benign and spontaneously resolving, mainly: pain, headaches, tachycardia, nausea, dizziness (14). We cannot distinguish the adverse events possibly associated with the local anesthetic, vasoconstrictor, care or apprehension.

Minimal local adverse effects. The addition of a vasoconstrictor to the anesthetic solutions can have local adverse effects. A non-blind comparative test including 32 patients, evaluated adrenaline + lidocaine versus mepivacaine only on the incidence, the postoperative haemorrhages and the local cicatrization after impacted wisdom teeth extraction (4). In "with adrenaline" group, the peroperative surgical blood losses were less, but bleedings were more numerous in postoperative (13 patients from 16 bled even 6 hours after the procedure, versus none in the "without adrenaline" group; p<0.0001) (4).

In the oral cavity area, we also know the risk of ischemic local necroses associated with the injection of a strongly adrenaline solution (concentration 1/50,000). This risk is as great as the site of injection is not very vascularised, as it is the level of the palatal mucosa (18,19). Systemic diffusion of adrenaline: no clinically tangible consequence.

Despite its vasoconstrictor effect, it is well established that the adrenaline contained in a dental use anesthetic cartridge can diffuse in general circulation (2,20). Several studies showed that, a few minutes after the oral injection of an adrenaline anesthetic solution, we note a significant increase in circulating adrenalin (2,2Q21).

A study with marked adrenaline showed that the increase concentration of adrenaline in the blood after dental anesthesia was mainly due to exogenous adrenaline, and not to the endogenous adrenaline, mainly secreted in the event of stress (21).

A pharmacokinetic study, undertaken among 18 patients in good health having to undergo the extraction of an impacted wisdom tooth, evaluated concentration of adrenaline in blood after the injection of three different anesthetic solutions of 2 ml each.

Lidocaine at 2 % with adrenaline at 1/80,000; or articaine at 4 % with adrenaline at 1/100,000; or articaine at 4% with adrenaline at 1/200,000 (each anesthetic solution was administered to 6 patients) (21). For 15 minutes after the injection, a significant increase in the blood concentration of adrenaline was noted (21).

A pharmacokinetic study, undertaken among 18 patients in good health having to undergo the extraction of an impacted wisdom tooth, evaluated concentration of adrenaline in blood after the injection of three different anesthetic solutions of 2 ml each: lidocaine at 2 % with adrenaline at 1/80,000; or articaine at 4 % with adrenaline at 1/100,000; or articaine at 4% with adrenaline at 1/200,000 (each anesthetic solution was administered to 6 patients) (21). For 15 minutes after the injection, a significant increase in the blood concentration of adrenaline was noted (21).

Some physiological effects of adrenaline. The cardiovascular and hemodynamic effects of the adrenaline contained in the dental use anesthetic solutions were the subject of studies since many years (2,22).

c- For example, a case of hypertensive crisis was reported, with dyspnoea, pulmonary oedema, and myocardial infarction in accordance with a local anesthesia by mepivacaine strongly proportioned in corbardin (aka levonordefrin, a sympathomimetic close to noradrenaline) for dental care. This accident occurred several minutes after the injection, to a 57-year-old coronary, hypertensive and diabetic man (ref 35).

d-According to Article R5144-19 of the Public Health Code, dental surgeons are required, like other prescribers and pharmacists, to declare to a regional drug monitoring centre any severe or unexpected adverse effect likely to be due to a medication -
e- This study was conducted by means of a questionnaire sent to dental surgeons in random cities. They had to collect for each of the first 3 patients who would undergo a local anesthesia, the medical history, the type of dental care, the anesthetic used (articaine for more than 90% of the patients), and the potential adverse events observed. Of the 1,600 dental surgeons contacted, 911 returned 2,731 usable questionnaires.

Close to half of the patients included presented risk factors (cardiovascular diseases, allergic ground, diabetes, etc). The global incidence of the undesirable events was slightly higher for the patients with risk (5.7% versus 3.5% for the other patients) (ref. 17).
Local anesthetic solutions for dental purposes

Limiting the pain of the dental procedure using a local anesthesia is an old concern.

A century of development. In the absence of anesthesia, the medical or dental surgical acts represented a real challenge, as well for the patient as for the practitioner confronted with the pain of his patient.

In October 1884 in Vienna, Karl Koller, an ophthalmologist, described for the first time the use of cocaine (by instillation) as a local anesthetic agent for a surgical procedure (1,2).

The same year, W Halsted performed for the first time the injection of a local anesthetic, by infiltration of cocaine on a nervous trunk of the oral cavity (the syringe as a medical instrument had been developed in the 1850’s) (1,2).

Very quickly cocaine, too concentrated, turned out to be dangerous, because of its cardiovascular toxicity. 13 fatal accidents were reported during the first seven years of use (1).

The development, in 1905, of the first synthetic local anesthetic responded to the demand for a less toxic substance: procaine, which quickly became the reference. Compared with cocaine, procaine is mainly not very toxic, but with a rather low anesthetic power and a short duration. The addition of adrenaline (discovered in 1903) made it possible to accentuate the effects (2).

Until about the year 1940, similar substances were synthesized, such as tetracaine, propoxycaine and chloroprocaine. But the report of frequent allergies with this anesthetic, ester type, started again the search for a safer local anesthetic (1).

In 1943, lidocaine was synthesized: it made it possible to obtain a fast anesthesia (in a few minutes), major and for a duration responding well to the needs and to complexity of modern odontostomatologic procedures (1). Thereafter, other chemically substances related to lidocaine were synthesized, mepivacaine, then prilocaine and articaine at the beginning of the 1970’s.

Currently, the synthesis of new local anesthetics no longer responds to essential requirement in odontostomatologie (1). Today in France, there are 3 local anesthesia solutions marketed for the dental use: articaine, lidocaine, and mepivacaine.

A standardized conditioning for easy handling. Currently, anesthetics for dental use are presented only in the form of injectable solution, packaged in “cartridges” of glass, for a single use, with a volume of about 1.8 ml. The "traditional" glass ampoules are not marketed any more because of the additional handling that they involved.

All anesthetic solutions are available either non-associated, or associated with a vasoconstrictor. This vasoconstrictor is generally adrenaline (aka epinephrine), more rarely noradrenalin (aka noradrenaline), even corbadrine (aka levonordefrin).

Preservative agents (sulfites) supplement the composition of a good number of anesthetic cartridges for dental use, in particular those containing a vasoconstrictor. It is necessary to take this into account for the patients allergic to these preservative agents A frequent use During dental care, the use of the local anesthesia is very frequent.

We estimate that more than three quarters of the French market of local dental anesthetic are represented by articaine. About 25 million cartridges of articaine are used each year in France, i.e. about 30 million cartouches all anesthetics combined (a) (3).

These figures, very important, can be matched with those of other countries: 11 million anesthetic cartridges used in 1993 in Ontario (for ten million inhabitants); 70 million cartridges per annum, 1970 to 1979, in Great Britain, there are about 250,000 daily injections in the British dentist’s surgeries (3,4).

Sterilizable “with cartridge” syringes. The use of local anesthetics in odontostomatologie resorts to a particular injection device: a specific "with cartridge" syringe model (b). The existence of single-use "with cartridge" syringes delivered in sterile packing, the possibility to sterilize syringes with a chrome steel cartridge, and the use of single-use sterile needles must make it possible to perform the anesthetic procedure under sufficiently hygienic conditions (c).

In practice, to limit the septic risk, all used cartridges, even partially used, absolutely must be thrown away. For most dental care, an anesthetic cartridge is sufficient; some oral surgery procedures can require 2 even 3 anesthetic cartridges.

A simple but non-ordinary anesthetic technique. Local anesthesia in odontostomatologie is akin to an anesthesia by infiltration which consists of depositing by means of a needle the anesthetic substance close to the nervous paths, and to thus obtain an anesthetisation of a limited territory (2).
These studies, carried out in general in a context of dental care with subjects being in otherwise good health, showed that the adrenaline contained in the anesthetic solution could increase the heart rate and blood pressure, for the adult as well as the child (2;22).

The metabolic effects of the adrenaline used in dental anesthesia are very limited: slight drop in the kalaemia (23) ; rise in the glycaemia (24). Thyrotoxicosis, barely detectable, have low amplitude and it is not shown that they have clinical consequences.

To our knowledge, no harmful clinical effects were shown in diabetics (f).

In therapeutic doses, few risks among cardiac patients. In the dental field, there are few studies available that have evaluated the risks associated with the systemic diffusion of adrenaline in patients with cardiovascular risk (25 to 30). According to a methodical synthesis published in 2002, 5 studies evaluated the effect of adrenaline among hypertensive patients within the context of a dental anesthesia (30). A slight transitory increase in blood pressure was generally noted during the dental anesthesia, barely detectable, than in the event of anesthesia without vasoconstrictor. A recent study attempted to evaluate these risks among 27 patients presenting various cardiac pathologies, and having to undergo dental care (g) (29). Each patient received 1 cartridge of anesthetic (i.e. 1.8 ml of lidocaine with adrenaline at 1/80,000), representing maximum 22.5 µg of adrenaline, which means approximate the equivalent of 4 cartridges of 1.8 ml adrenaline at 1/200,000 during one session of treatment (13,28). This number of cartridges is never reached during current dental care. No drug interaction at the doses used. Taking into account vasoconstrictors’ alpha and beta adrenergic effects (more or less specific), the injection of an adrenaline (or noradrenaline) anesthetic solution exposes to potential interactions with certain drugs. Three classes of drugs are in principle concerned: antidepressants, beta-blockers, and certain nerve sedatives (phenothiazines in particular) (i) (28, 31, 32). However, currently there are no reported cases of clinically harmful drug interaction, during current dental care, with these various drugs (15, 28). And there is no formal contra-indication with these drug associations during dental care, with the amounts of adrenaline used in current practice (32, 33).

Practical Conclusion: no contra-indication
In the dental field, for many years, it has been customary practice to associate a vasoconstrictor with the anesthetic solution.

Despite the few comparative tests available, this vasoconstrictor seems to improve the effectiveness and increase the duration of the local anesthesia. Whether it is for dental care or oral surgery procedures, the concentration of 1/200,000 adrenaline seems as effective as higher concentrations. It has not been shown that the addition of adrenaline to the local anesthetics increases the risks of adverse effects, for the quantities regularly used: Noradrenaline does not have a demonstrated advantage against adrenaline and exposes to a rare risk of severe hypertension.

For practice, anesthetic solutions containing a 1/200,000 concentration of adrenaline have the best benefit-risks balance and can be used for current dental treatment. A cardiac disorder does not constitute a contra-indication.

Synthesis processed collectively by the Editing staff of Prescrire magazine
f- The presence of adrenaline in dental anesthetic solutions is sometimes the subject, in France, of "precautions for use" for diabetics (ref. 36,37). No specific, usage precautions for diabetics are mentioned in the United Kingdom nor in the United States of America (ref. 12,38). The description of a possible peak of (moderate and transient) hyperglycaemia during an adrenaline dental anesthesia does not present in fact any specific risk for the diabetic. For a procedure as specific as a dental anesthesia, hyperglycaemia would represent, on the other hand, a risk much more significant for this type of patient. We have not found either any specific clinical data making it possible to identify a tangible risk for local anesthetics for the diabetic in the oral cavity.

h- In this study, the 27 patients presented either a coronary insufficiency, or a cardiac insufficiency, or an aortic wall pathology. 18 patients were treated by a beta blocker (ref. 29).

i- Theoretically, the risk is cardiovascular. The complications can result in a paroxysmal hypertension with possibilities of heart rhythm disorders for antidepressants, a hypertension and a bradycardia for beta-blockers, and a hypotension associated with a reflex tachycardia for phenothiazines (ref. 20, 31, 32).

Documentary research
Our documentary research performed a continuous prospective follow-up on the main international reviews and Current Contents-Clinical Medicine implemented within the documentary research centre Prescrire, as well as on the systematic consultation of basic clinical pharmacology works (Martindale The Complete Drug Reference 33rd ed, etc.). We interrogated the data bases Cochrane (2003 issue 1), Embase/Excerpta Medica Drugs and Pharmacology (1989 - 1st quarter 2003), Medline (1966 - February week 3, 2003), Réactions (1983 - January 2003), as well as Internet sites of the following organizations: ADA, AHRQ, ANAES, Bibliodent, BML, INAHTA, Infobanque AMC, NGC, NICE, NIH, SIGN, for the last time on 4 March 2003.

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