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Adverse Drug Reactions to Local Anaesthetics

A Review of the French Pharmacovigilance Database

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Abstract

Background: Some evidence of significant patient morbidity or mortality has been reported with the use of local anaesthetics (LAs). The most common adverse drug reactions (ADRs) to LAs are neurological (seizures) and cardiac (conduction disorders, cardiac arrests). However, little is known about other adverse drug reactions (ADRs).

Objective: The aim of this study was to characterize the safety profile of the LAs lidocaine, bupivacaine, mepivacaine, ropivacaine and levobupivacaine.

Study design: We studied ADRs occurring between 1995 and 2006 reported to the French Pharmacovigilance System.

Main outcome measure: For each ADR, we noted type of LA, type of ADR, its seriousness and the causality assessment score.

Results: We identified 727 reports (corresponding to 0.3% of patients in the database) in which LA was suspected as the cause of 1157 different ADRs. Sixty-one patients (8.7%) were children aged <18 years. Lidocaine (36.0%) and bupivacaine (35.4%) were the LAs most often involved. The most frequently reported ADRs were failure of the block (27.7%), followed by neurological (22.1%), allergic (19.4%) and cardiovascular (15.3%) complications. Eight patients died. Spinal anaesthesia performed with bupivacaine represented 90% of failed blocks. Seizures were the most frequent neurological complications, leading to death in four cases. Twenty-two of 111 cardiovascular complications were cardiac arrest (three of which were fatal).

Conclusion: To our knowledge, this is the first analysis of safety profiles of LAs in a non-selected population, using data collected in a pharmacovigilance database. The present study confirmed the frequency and seriousness of both

neurological and cardiovascular complications. Other less well documented ADRs were identified, such as spinal anaesthesia failures with bupivacaine and allergic reactions following LA injections.

Background

Local anaesthetics (LAs) are widely used for local or regional anaesthesia techniques. Lidocaine (lignocaine) and bupivacaine have been in use for more than 50 years and, more recently, drugs such as mepivacaine, ropivacaine and levobupivacaine have been launched on the market. Because of the development of regional anaesthesia techniques over the past few years, the use of LAs is increasing worldwide.[1-5] However, prospective studies have provided evidence of significant patient morbidity and mortality associated with the use of these drugs.[6-13] The most common adverse drug reactions (ADRs) to LAs are neurological (seizures) and cardiac (conduction disorders, cardiac arrests).[8,14-21] Such ADRs are related to the pharmacological properties of this drugs, mainly the membrane-stabilizing effects.[22] However, little is known about other types of ADRs. In light of this information, our aim was to characterize the profiles of ADRs associated with the use of lidocaine, bupivacaine, mepivacaine, ropivacaine and levobupivacaine, drawing on the French Pharmacovigilance System database.

Methods

The French Pharmacovigilance System consists of a network of 31 regional drug pharmacovigilance centres. The French Pharmacovigilance Database was established in 1985 to register spontaneous reporting of ADRs. By law, every prescriber, physician, dentist or midwife must report 'serious' or 'unexpected' ADRs to their French Regional Pharmacovigilance Centre. A 'serious' ADR is defined as an adverse effect that is fatal or life threatening, that causes hospitalization or prolongation of hospitalization, or permanent or significant disability (recommendations of the International Committee on Harmonization from the WHO Collaborating Centres for International Drug Monitoring). An 'unexpected' ADR is defined as an ADR whose nature or severity is not consistent with data contained in domestic labelling or market authorization of the drug. All reported ADRs are analyzed and validated by the Regional Pharmacovigilance Centre before being registered into the French Pharmacovigilance Database. In the present study, we studied ADRs occurring between 1 January 1995 and 31 December 2006 that were reported to the French Network of Pharmacovigilance Centres (and recorded into the French Pharmacovigilance Database). Among the 210 017 ADRs reported, we selected those in which the LA was considered as 'suspect'. For each ADR we noted year, patient age and sex, type of LA and type of ADR (clinical symptoms, seriousness and outcome) as well as the imputability score.[23,24] The seriousness of the ADR was assessed by pharmacovigilance centres before being recorded in the database, according to the International Conference on Harmonisation definition.[25] The imputability score is the assessment of the probable responsibility of a drug in the development of an undesirable effect. This is measured by the French imputability method based on to the time to onset, the course of the reaction ('C' = chronological subscore), risk factors and screening for other causes ('S' = semiological subscore). According to the values of these two subscores (C and S), intrinsic imputability is classified into five levels (I0–I4): 'unlikely', 'possible', 'probable', 'likely' and 'certain'.[24] Only reports with an imputability score of at least 'possible' were analyzed.

Results

In the database, 210 017 ADRs were registered between 1995 and 2006. Among those, we identified 727 reports (0.3% of the total) in which LA was suspected as the cause of 1157 ADRs. Patients

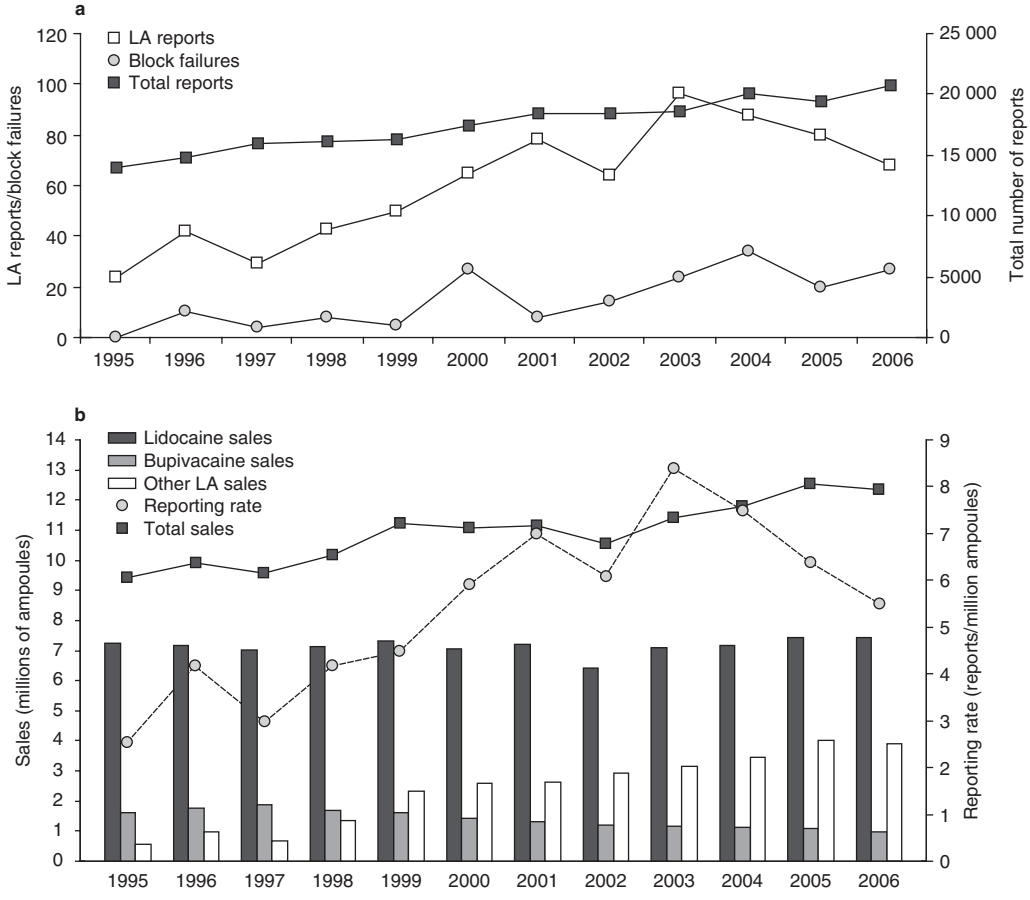

Fig. 1. (**a**) Total number of ADR reports, number of ADR reports involving local anaesthetics (LAs) and the number of block failures with LAs in the French Pharmacovigilance Database from 1995 to 2006. (**b**) Total sales of all LAs and of lidocaine, bupivucaine and other LAs (ropivacaine, mepivacaine and levobupivacaine) from 1995 to 2006; number of ADR reports (including block failures) for all LAs per million ampoules sold.

included 448 women and 279 men. Mean age ± SD was 49 ± 22 years (range 1 day–99 years). Sixty-one patients (8.7%) were children aged <18 years. Figure 1a shows the total number of reports in the database, the number of reports involving LAs and the number of block failures with LAs from 1995 to 2006. We observed a slight increase in reports involving LAs during this period. Simultaneously, the use of LAs increased during the same period (figure 1b shows the evolution of total sales of all LAs available in France, lidocaine, bupivacaine and other drugs [ropivacaine, mepivacaine and levobupivacaine]). The number of reports per million ampoules increased during the study period (×2.2 between 1995 and 2006, figure 1b) with no difference between the different LAs (data not shown). Table I presents the main characteristics of the reports for each drug according to the seriousness and type of ADRs. The mean number of drugs involved in each report involving LAs was 2 ± 1.7 (range 1–13) and the mean number of ADRs per report was 1.6 ± 1 (1–6). Lidocaine and bupivacaine were the LAs most often involved (262 reports [36.0%] and 257 reports [35.4%], respectively) followed by ropivacaine (76 reports [10.4%]), mepivacaine (62 reports [8.5%]) and levobupivacaine (4 reports in 2006 [0.6%]) [table I]. In approximately half of the reports, LA was the

Table I. Main characteristics of the reports for each drug according to the seriousness and type of adverse drug reactions

Reports	Total[a]	Lidocaine[a]	Mepivacaine[a]	Bupivacaine[a]	Ropivacaine[a]	Levobupivacaine[a]	Combination[a,b]
No. of reports	727	262	62	257	76	4	66
Serious	322 (44.2)	119 (45.3)	18 (29)	95 (36.9)	55 (72.3)	1	34 (51.5)
hospitalization	201 (27.6)	74 (28.2)	13 (21)	71 (27.6)	31 (40.8)	0	12 (18.2)
permanent incapacity	27 (3.7)	1 (0.4)	2 (3.2)	6 (2.3)	2 (2.6)	0	16 (24.2)
life threatening	86 (11.8)	41 (15.6)	3 (4.8)	16 (6.2)	19 (25)	1	6 (9.1)
death	8 (1.1)	3 (1.1)	0	2 (0.8)	3 (3.9)	0	0
Type of ADRs							
Block failure	201 (27.7)	5 (1.9)	8 (12.9)	181 (70.4)	5 (6.6)	0	2 (3.1)
Neurological	161 (22.1)	66 (25.2)	16 (25.8)	28 (10.9)	36 (47.4)	4 (100)	10 (15.2)
Allergic	141 (19.4)	94 (35.9)	16 (25.8)	18 (7.0)	4 (5.3)	0	9 (13.6)
Cardiovascular	111 (15.3)	51 (19.5)	18 (29.1)	17 (6.6)	17 (22.4)	0	8 (12.1)
Sensorial system	43 (5.9)	4 (1.5)	2 (3.2)	1 (0.4)	1 (1.3)	0	36 (54.5)
Respiratory	20 (2.8)	14 (5.3)	0	4 (1.6)	1 (1.3)	0	1 (1.5)
Skin	17 (2.3)	12 (4.6)	0	0	5 (6.6)	0	0
Other	33 (4.5)	16 (6.1)	2 (3.2)	8 (3.1)	7 (9.1)	0	0

a Data are expressed as number (%).

b Mixture = association of local anaesthetics (lidocaine + ropivacaine = 4, lidocaine + mepivacaine = 1, lidocaine + bupivacaine = 47, bupivacaine + ropivacaine = 4, mepivacaine + ropivacaine = 4, mepivacaine + bupivacaine = 6).

only drug involved in the ADRs (393 reports [54.1%]).

The most frequently reported ADRs were failure of the block (n = 201, 27.7%) followed by neurological (n = 161, 22.1%), allergic (n = 141, 19.4%) and cardiovascular (n = 111, 15.3%) ADRs (table I). Approximately half of these ADRs were serious (n = 322, 44.2%) and outcomes were favourable in most cases (n = 593, 83.4%).

Eight deaths (1.1%) with an imputability score of at least possible for the LA occurred during the study period (seven females, including an infant aged 1.6 years and a newborn baby, and a male newborn baby) [table II]. LA was the sole drug involved in three cases and death occurred with lidocaine, bupivacaine and ropivacaine. Seizures were the most common ADRs leading to death. Death occurred after spinal anaesthesia (three cases), peripheral nerve blocks (three cases), oral ingestion (one case) and inadvertent intravenous injection (one case).

Block failure was the most frequent ADR reported (n = 201, 27.7% of reports) and the number of instances of block failure increased from 2002 onwards (table I, figure 1a). Block failure was defined as insufficient or inadequate sensory block, leading to general anaesthesia prior to surgery. Thus, technical failures were excluded from the study. Patients (55% women and 45% men) were aged 53 ± 20 years. In 90% of cases (n = 181) the failed block was a spinal anaesthesia performed with bupivacaine, with a generic drug in 53% of these cases (n = 96). In 91% (165 of 181), bupivacaine was the sole drug involved. No technical problems occurred during the puncture and in all cases the anaesthesiologist mentioned a backflow of cerebrospinal fluid and correct injection of LA. Because of the lack of a sufficient sensory block or no block at all, a general anaesthesia had to be performed. The other failures concerned lidocaine (five local anaesthesiae), mepivacaine (four local anaesthesiae, two sub-Tenon's blocks, one peripheral nerve block), ropivacaine (five epidural anaesthesiae) and a mixture of lidocaine + bupivacaine (two epidural anaesthesiae).

Neurological adverse effects were the second most commonly reported ADRs (n = 161, 22.1% of cases [table I]). Seizures (generalized tonic-clonic convulsions or generalized convulsive status epilepticus, i.e. an epileptic seizure that is sufficiently prolonged or repeated at brief intervals)

were the most frequent neurological complications (21.2% of the neurological cases), followed by peripheral nerve damage (9.9%), psychiatric disorders (agitation 6.4%, confusion 5.3%), dysarthria (4.6%), paralysis (3.9%) and drowsiness (3.5%). The four reports involving levobupivacaine described neuropathy occurring after peripheral nerve blocks (three cases) or local anaesthesia (one case). Three cases of meningitis were reported by three different centres: two in women after a spinal anaesthesia (one case, 23-year-old patient) or an epidural (one case, 45 year-old patient) anaesthesia and one in a 17-year-old man after a spinal anaesthesia. A positive outcome was noted in each case.

In total, 60 cases of seizures were reported with three cases of generalized convulsive status epilepticus. In four cases of seizure, a cardiac arrest occurred, resulting in two deaths. The annual incidence of seizure reports varied from 1 to 10, with a slight increase after 2002. These seizures occurred equally often in men and women, mean age 41 ± 28 years (range 1 day–85 years). In 18 cases (30%) the seizures affected children aged <18 years. The LAs most frequently involved were lidocaine (26 cases, 43%) followed by ropivacaine (18 cases, 30%) and bupivacaine (7 cases, 12%). A mixture of LAs was encountered in five cases (8%). In 55% of cases, LA was the sole drug noted in the report. LAs were used for local anaesthesia (20 cases), peripheral nerve blocks (19 cases) and spinal anaesthesia (7 cases). In five cases, seizures occurred after direct intravenous injection. A life-threatening complication or death occurred in 15 (25%) and 4 (7%) cases, respectively.

Allergic manifestations were the third most frequently reported ADRs (n = 141, 19.4% [table I]). Oedema was the most frequent complication (29%, with 8% of oedema in the neck area), followed by skin eruptions (28%), anaphylactic reactions (14%) and urticaria (13%). All of the five LAs included in this study were involved in allergic manifestations, and the annual incidence varied between 6 and 18 cases per year. Women were most frequently involved (99 cases, 70%). A life-threatening complication occurred in 27 cases. LA was the sole drug encountered in 45 cases (32%). LA was the cause in 14 cases, determined either by positive skin testing (preservatives such as bisulfite were excluded from the analysis) or by symptoms occurring after LA injection. This led to a frequency

Table II. Details of the eight deaths that occurred during the study period with an imputability score of at least 'possible' for the local anaesthetic

No.	Y	Sex	Age (y)	Concomitant drugs	LA	Administration route	ADR	Imputability score[a]
1	1999	F	1.6		Lidocaine	Buccal	Seizures, cardiac arrest	Likely
2	2001	F	32		Ropivacaine	Accidental intravenous	Seizures, cardiac arrest	Likely
3	2001	F	90		Ropivacaine	PNB	Cardiac arrest	Probable
4	2001	F	Newborn	Sufentanil	Ropivacaine	Spinal mother	Third AVB	Possible
5	1996	F	43	Heptaminol, amitriptyline, niflumic acid, misoprostol, dipotassium clorazepate	Lidocaine	Paravertebral infiltration	Seizures	Possible
6	2005	F	44	Midazolam, sufentanil, cisatracurium besilate, propofol	Ropivacaine	Peripheral nerve block	Third AVB, ventricular fibrillation	Possible
7	2001	F	80	Cefazolin, metoclopramide, buprenorphine, ketoprofen, methotrexate	Bupivacaine	Spinal	Shock, pancreatitis, liver failure, kidney failure	Possible
8	1999	M	Newborn	Paracetamol (acetaminophen), propofol, fentanyl, amoxicillin/clavulanic acid	Lidocaine	Spinal	Seizures	Likely

a Imputability is classified into five levels (I0–I4): 'unlikely', 'possible', 'probable', 'likely' and 'certain'.[24]

ADR = adverse drug reaction; **AVB** = atrio-ventricular block; **F** = female; **M** = male; **PNB** = peripheral nerve block.

Table III. Details of the 14 allergic adverse drug reactions (ADRs) caused by local anaesthetics

No.	Year	Sex	Age (y)	Concomitant drugs	Local anaesthetic	Administration route	ADR	Seriousness	Imputability score[a]
1	1996	F	49		Lidocaine	Local anaesthesia	Syncope	Life threatening	Likely
2	1998	F	32		Mepivacaine	Local anaesthesia	Neck oedema	Life threatening	Likely
3	2001	M	64		Lidocaine	Local anaesthesia	Anaphylactic shock	Life threatening	Likely
4	2004	M	33		Lidocaine	Local anaesthesia	Anaphylactic shock, cardiac arrest	Life threatening	Possible
5	2004	F	24		Lidocaine	Peripheral nerve block	Eczema	Not serious	Certain
6	1996	F	44		Lidocaine	Local anaesthesia	Generalized eruption	Not serious	Likely
7	1998	F	51		Lidocaine	Local anaesthesia	Generalized eruption	Not serious	Likely
8	2001	F	42		Lidocaine	Local anaesthesia	Oedema	Not serious	Likely
9	2001	F	54		Mepivacaine	Local anaesthesia	Urticaria	Not serious	Certain
10	2002	F	36		Lidocaine	Local anaesthesia	Generalized erythema	Not serious	Possible
11	2004	F	35		Lidocaine	Epidural anaesthesia	Eruption, pruritus	Not serious	Certain
12	2002	M	87		Mepivacaine	Local anaesthesia	Local oedema	Not serious	Possible
13	2001	F	63	Hexamidine	Lidocaine	Local anaesthesia	Neck oedema	Not serious	Likely
14	2005	M	50	Midazolam, sufentanil	Mepivacaine	Peripheral nerve block	Anaphylactic shock	Prolonged hospitalization	Certain

a Imputability is classified into five levels (I0 to I4): 'unlikely', 'possible', 'probable', 'likely' and 'certain'.[24]

F = female; **M** = male.

of LA-induced allergic reactions of 2% of the 727 ADR reports involving LAs over the study period. These 14 cases are detailed in table III.

Cardiovascular complications were the fourth most frequently reported ADRs (n = 111, 15.3% [table I]). Chest discomfort was the most frequent cardiac ADR (25.4%) followed by hypotension (11.2%), cardiac arrest (22 cases, 10.7%), bradycardia (9.3%), tachycardia (8.3%) and circulatory shock (7.8%). The 22 cardiac arrests occurred in 12 women and 10 men with a mean age of 38.5 ± 22 years (range 8 months–50 years). In three cases, patients were children aged <18 years. Ropivacaine was the most frequently involved LA (ten cases). A lidocaine + bupivacaine combination was encountered in two cases. In the majority of cases, LA was the sole drug involved. Death occurred in three cases. The cardiac arrests are detailed in table IV.

Respiratory ADRs represented 2.8% of all cases (20 cases). Dyspnoea was the most frequent symptom reported (34.5%) followed by bronchoconstriction (16.4%) and newborn or adult respiratory arrests (12.7% and 7.3% of cases, respectively). In all cases the outcome was favourable. Bronchoconstriction concerned nine patients (six women and three men) with a mean age of 43 ± 24 years (range 12–77 years). LA was the sole drug involved in five cases (one mixture of LAs). Lidocaine was reported in eight cases. Life-threatening complications or prolonged hospitalization occurred in six cases (three cases each). These ADRs occurred after local anaesthesia (three cases), intravenous injections (two cases) or peripheral nerve blockade (one case).

Table IV. Details of the 22 cardiac arrests reported during the study period

No.	Year	Sex	Age (y unless otherwise specified)	Concomitant drugs	Local anaesthetic	Administration route	ADR	Seriousness	Imputability score[a]
1	2000	F	33		Ropivacaine	Epidural anaesthesia	Asystole	Life threatening	Likely
2	2005	F	44	Cisatracurium besilate, sufentanil	Ropivacaine	Peripheral nerve block	Ventricular fibrillation	Death	Possible
3	2006	M	42		Ropivacaine	Local anaesthesia	Seizures	Life threatening	Possible
4	1998	F	44	Fentanyl	Lidocaine + bupivacaine	Combined spinal-epidural anaesthesia	Bradycardia	Life threatening	Likely
5	2004	F	8 mo	Ornidazole, sufentanil, sulpiride	Ropivacaine	Epidural anaesthesia	Bradycardia	Life threatening	Likely
6	2002	F	67		Ropivacaine	Peripheral nerve block	Ventricular fibrillation	Life threatening	Likely
7	2004	F	43	Nifedipine + atenolol, ketamine, perindopril, triamcinolone	Ropivacaine	Epidural anaesthesia	Asystole	Life threatening	Likely
8	2006	F	65	Cefazolin	Ropivacaine	Peripheral nerve block	Asystole	Life threatening	Likely
9	2001	F	54	Propofol, alfentanil, atropine	Lidocaine	Local anaesthesia	Bradycardia	Life threatening	Possible
10	2004	M	2	Sevoflurane	Lidocaine + bupivacaine	Local anaesthesia	Asystole	Life threatening	Possible
11	2004	M	55		Lidocaine	Local anaesthesia		Life threatening	Likely
12	1995	F			Bupivacaine	Epidural anaesthesia	Bradycardia	Permanent incapacity	Probable
13	2005	M	4.5		Lidocaine	Spray	Bradycardia	Life threatening	Probable
14	2004	M	28		Lidocaine	Local anaesthesia	Seizures + ventricular fibrillation	Life threatening	Possible
15	2005	M	36	Suxamethonium-chloride, sufentanil, sevoflurane, thiopental, ondansetron	Ropivacaine	Peripheral nerve block	Ventricular fibrillation	Life threatening	Possible
16	2006	M	60	Midazolam, hydroxyzine, flecainide	Mepivacaine	Peripheral nerve block	Asystole	Permanent incapacity	Possible
17	2001	F	90		Ropivacaine	Peripheral nerve block	Asystole	Death	Probable

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Table IV. Contd

No.	Year	Sex	Age (y unless otherwise specified)	Concomitant drugs	Local anaesthetic	Administration route	ADR	Seriousness	Imputability score[a]
18	2001	F	44		Lidocaine	Local anaesthesia	Seizures	Unknown	Possible
19	1998	M	32		Bupivacaine	Spinal anaesthesia	Vasovagal syncope	Life threatening	Possible
20	1999	M	42	Midazolam, propofol, alfentanil	Lidocaine	Intra-articular	Bradycardia	Life threatening	Possible
21	2001	F	32		Ropivacaine	Accidental intravenous	Seizures	Death	Likely
22	2004	M	33		Lidocaine	Local anaesthesia	Anaphylactic shock	Life threatening	Possible

a Imputability is classified into five levels (I0–I4): 'unlikely', 'possible', 'probable', 'likely' and 'certain'.[24]

ADR = adverse drug reaction; **F** = female; **M** = male.

Discussion

The present study was performed to characterize ADRs related to LAs and to investigate whether the profile of these ADRs could improve our knowledge in this area. While interest in regional anaesthetic techniques is still growing worldwide there are few studies in the literature focusing on complications. Because it would be difficult to thoroughly address all complications of regional anaesthesia in one review, specific and/or serious complications are the most reported ones. For the first time to our knowledge, our study reports an approach of analyzing complications related to LA use in the generalized population (i.e. from neonates to adults) and during a long period of time.

It is interesting to note the 2-fold increase in the reporting rate during the study period. This increase could be due to a better reporting of ADRs to the French Pharmacovigilance System, thus suggesting a better efficiency of this drug monitoring programme. Another explanation could be the increased use of the newest LAs from 1999 (i.e. mepivacaine, ropivacaine, levobupivacaine), added to by a potential Weber effect.[26] Although these data should be interpreted with caution, we noted a peak in the reporting rate in 2003, followed by a slight decrease (figure 1b). This decrease could be explained by both the publication of specific guidelines from the French Society of Anaesthesiology and Intensive Care[27] and that of serious case reports after LA injections.[6,8,9,11-13]

Previous studies on the same topic usually focused on a specific complication or type of LA, occurring in a selected population. Moreover, anaesthetists involved in such studies were usually selected after giving their consent, thus introducing a potential selection bias.

Even though the outcome was favourable in many cases, ADRs reported in our study were often serious (44.2%), leading to death in eight cases (1.1%). These results are very similar to the 44.8% of ADR reports considered as serious in the overall French Pharmacovigilance Database (1.7% for deaths).[28] However, the percentage of ADRs that resulted in persistent or significant

disability/incapacity (3.7% vs 1.7%) or that were life threatening (11.8% vs 4.1%) was higher with LAs than with other drugs. Thus, the safety profile of LAs is possibly less favourable than that currently expected by anaesthesiologists, even though they are in very frequent use. It is well documented that LA systemic toxicity can lead to cardiac arrest and death. Auroy et al.[8] reported that fatal LA toxicity is a rare but dramatic complication and mainly concerns older people. However, in our study, three of eight cases referred to children or neonates. Another important difference between the study by Auroy et al. and ours is that spinal anaesthesia was not the only route of administration of LA leading to fatal toxicity. In our study, this occurred with every type of route of administration. These differences could be explained by the design of the two studies. In Auroy's study, anaesthesiologists who accepted to participate in the study had to report immediately any serious adverse event they had encountered after a regional anaesthesia by calling a telephone 'hotline'. On the other hand, reporting to the French Pharmacovigilance Database is anonymous and this could make reporting easier, particularly when dramatic complications occur in young people. Moreover, the causality assessment is made by a trained medical doctor or a pharmacist at the level of the regional pharmacogivilance centres and not by the health professional reporting the case, or the patient himself, as occurs in other countries. Thus, the French Pharmacovigilance System constitutes an essential tool for routine practice with quality control provided at each reporting stage: only healthcare professionals can report, and causality criteria are assessed for each drug-ADR pair by pharmacovigilance professionals.[28] Our results highlight the importance of publishing guidelines to define best practices when using LAs and, thus, to decrease the risk of such complications. However, even when procedures are followed correctly, human error can never be totally removed, as illustrated by the accidental intravenous injection (table II). It is interesting to note that ropivacaine was the LA most frequently involved in cardiac arrests. However, it also appears to be the long-acting LA with the best safety profile.[19] This probably explains why, in France, its use is favoured over that of bupivacaine for performing peripheral nerve blocks or epidural anaesthesiae.

Surprisingly, block failure was the most frequent ADR reported to the French Pharmacovigilance System, with an increase until 2002. Block failure is well documented after peripheral nerve blocks, its incidence depending on the block performed.[21] Failure rates after brachial plexus anaesthesia are usually approximately 3–5%, even when performed by very well practiced anaesthesiologists. Central neuraxial (spinal or epidural) block failures are less well documented in the literature (mostly case reports[29]). Thus, they are less well accepted by anaesthesiologists. This could explain the surprisingly high rate of spinal block failures encountered in our study. The French Pharmacovigilance Database reports are based on ADRs. The failures reported, therefore, occurred after LA was injected, thus excluding a technical problem while performing the spinal anaesthesia. Bupivacaine was the only LA licensed for intrathecal injections in France until 2006, and it is the main LA with which this specific complication is reported. Spinal lidocaine injections produce deficits (transient neurological symptoms, cauda equina syndrome) when administered in clinically used concentrations, whereas bupivacaine is considered the least neurotoxic.[30] Intrathecal lidocaine injection is, therefore, contraindicated in most countries. Dose miscalculations, use of inert LA, anatomical malformations and enlarged thecal volumes are the main explanations advanced in the literature.[31-34] A generic drug was involved in the majority of cases. Thus, its role remains questionable and further studies are mandatory to address this. Because they are rarely encountered from an individual point of view, their incidence is underestimated and few studies in the literature focus on the problem. In the present study, spinal block failures appeared to be the main ADR related to LAs. We are currently undertaking a prospective multicentre study to try and better investigate this issue.

Not surprisingly, neurological complications were the second most frequently reported ADRs. In many cases, lidocaine was the LA involved.

Seizures were the most common neurological complication. Seizures after LA administration are well documented in the literature.[8,14,17] Brown et al.[35] reported a higher incidence of seizures following brachial plexus blocks rather than epidural anaesthesia. Our results confirmed the higher frequency of seizures following peripheral nerve blocks rather than central neuraxial blocks. Both sexes and all ages were concerned by this ADR and it was considered a serious reaction in 32% of cases (life threatening or death). Among the other neurological complications described, there were three cases of meningitis. Infection is a rare complication of regional anaesthesia, although meningites have been reported following central neuraxial blockade.[36,37] The consequences are potentially dramatic, even though in our study the outcome was positive in all cases. The anaesthetist who performed the block often played an important role in the transmission of bacteria. Contamination usually occurred during the preparation for the technique. Meticulous adherence to sterile techniques is strongly recommended when performing central neuraxial blocks.

Serious, life-threatening allergic reactions to LAs are rare.[21] Their true incidence is still debated. However, it is well established that allergic reactions are more common following exposure to ester rather than amide compounds. Moreover, adrenergic reactions and panic attacks are often misdiagnosed as allergic reactions.[21] The main problem with characterizing allergic drug reactions in our study was the number of drugs involved in each report. We first excluded all reports where skin-prick testing was positive for a drug other than LA and all reports where skin-prick testing to LA was negative. This left us with 141 reports of allergic ADRs in which LA (alone or in combination with other drugs) could be responsible. We were able to identify 14 reports in which the causality assessment between LA and allergic reaction was 'likely'. In the majority of these cases, skin-prick testing confirmed the role of LA. Even though allergic reactions to LAs are rare, anaesthesiologists must keep in mind that they do occur. Recommending skin-prick testing with LAs could be reasonable when allergic reactions have occurred following LA administration. The fact that many of the 14 allergic reactions confirmed by skin-prick testing or by symptoms occurred in recent years could be a positive indication that anaesthetists are exploring cases of allergic reactions associated with LAs, in line with guidelines.

The main limitations of our study are the difficulty in evaluating the causality of an ADR to LAs even when, as in 53% of reports, LAs are the only drugs involved, and the problem of under-reporting. Even though by law all ADRs should be reported to the Pharmacovigilance System, Begaud et al.[38] estimated that approximately 5% of serious ADRs are actually reported. Spontaneous reporting of ADRs is still the most frequently used and efficient method to identify new ADRs after approval. The main limitation is that it is hampered by both quantitative and qualitative under-reporting.[28] However, the reporting rate in France is one of the highest among European countries,[39] with a reporting rate of 389.7 reports/10^6 population per year. Moreover, it has been shown that, whatever the magnitude of the under-reporting, it did not affect the results when comparing the same type of drugs (i.e. LAs).[40] In the present study, spontaneous reporting was well suited to highlighting specific problems encountered with the use of LAs that were not very familiar to many anaesthesiologists (i.e. spinal block failure).

Conclusion

In conclusion, the present study develops a novel approach of studying complications related to LA use. Some complications are life threatening, not only in the elderly population but also in young adults and children, and physicians must keep in mind that LAs can lead to death. Seizures and cardiac arrests still occur, emphasizing the need for specific usage guidelines to try and decrease their incidence. Surprisingly, block failure following spinal anaesthesia is not as rare as is thought. Further studies are needed to improve our knowledge of this area. Finally, allergic reactions related to LA compounds do exist and can justify the use of skin-prick testing.

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