Editorial
Potential neurotoxicity of local anaesthetic agents

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The local anaesthetic agent 2-chloroprocaine (Nesacaine) has recently been introduced in Canada, although it has been available in the United States for many years. Chloroprocaine is an amino ester local anaesthetic similar in structure to procaine, and has been characterized as an agent which produces a rapid onset and a relatively short duration of anaesthesia. Its prime clinical advantage appears to be its low systemic toxicity which is related to the rapid hydrolysis of this agent by plasmacholinesterase. Recently, the potential neurotoxicity of chloroprocaine has been the subject of considerable interest in the United States.

The neurotoxicity of local anaesthetic agents has concerned anaesthetists for many years. Although sporadic reports of local toxic reactions have appeared in the literature, large epidemiological studies have indicated that regional anaesthesia is a remarkably safe procedure, when properly performed.[1,2] The greatest concern regarding neurotoxicity involves the intrathecal use of local anaesthetics, since spinal cord damage in an otherwise healthy patient has catastrophic implications. However, epidemiological studies of spinal anaesthesia, primarily involving tetracaine and lidocaine, have indicated a remarkable safety record for this technique.[3–5] On the other hand, it is known that local anaesthetic agents are capable of causing local irritation and neurotoxicity at concentrations usually higher than are employed clinically.[6]

The concern regarding the potential neurotoxicity of local anaesthetics following intrathecal administration resurfaced in the United States following the reports of four cases of prolonged sensory/motor deficits which appeared to be related to the accidental subarachnoid injection of chloroprocaine.[7,8] Several factors served to focus attention on these reports: (1) All four cases occurred within a period of six months in 1979–1980. (2) Three cases occurred in one institution in Indiana while the fourth case occurred in California. (3) Most of the cases were believed to involve accidental subarachnoid injections of large doses of chloroprocaine which were intended for administration into the epidural space. (4) All patients were young healthy females with no history of previous neurologic abnormality. (5) A relationship appeared to exist between the dose of chloroprocaine administered and the severity of the neurological damage (Table I). Subsequent to these reports, five additional cases of apparent neurotoxicity following the use of chloroprocaine were reported in 1982.[9] These cases, however, occurred over a period of several years and do not appear temporally related to the initial four case reports. In addition, both bupivacaine and chloroprocaine were administered to several of these patients.

An editorial published in 1980 attempted to analyze the potential problem.[10] Based on the information available at that time, the following conclusions were drawn: (1) The neurotoxic reactions were apparently due to the inappropriate use of chloroprocaine. (2) The potential neurotoxicity of large doses of chloroprocaine administered intrathecally could not be ruled out. (3) The pH of commercial chloroprocaine solutions is significantly lower than that of other local anaesthetic solutions and may have contributed to these adverse responses. It was recommended that additional animal studies should be conducted to clarify the potential neurotoxicity of chloroprocaine. Moreover, use of an adequate test dose and the

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TABLE I Summary of initial reports of prolonged sensory/motor deficits following the use of 2-chloroprocaine

Case	*Ref*	*Total dose of chloroprocaine (mg)*	*Duration of sensory/motor deficit*
18-yr-old female	7	360	72 hrs
34-yr-old female	7	480	>4 wks
29-yr-old female	7	540	6 mon
33-yr-old female	8	840	>9 wks

administration of fractional doses of local anaesthetics for epidural administration were recommended, if possible, to avoid accidental subarachnoid administration of large doses of local anaesthetics. Finally, it was also suggested that, if possible, spinal fluid should be withdrawn following the known intrathecal administration of large amounts of local anaesthetics, in order to decrease the local anaesthetic concentration in cerebrospinal fluid.

Since these initial case reports, considerable interest, controversy and emotion have been generated concerning the potential neurotoxicity of chloroprocaine. The scientific studies that have been conducted to clarify this issue are unfortunately contradictory. Moreover, to date little of the data has been published in refereed journals. Those studies which have been reported are summarized in Table II. Two studies have examined local tissue reactions to peripheral nerves exposed to various local anaesthetic agents. Barsa *et al.* observed rather severe irritant effects following exposure of the rabbit vagus nerve to chloroprocaine, but not to lidocaine or bupivacaine.[11] On the other hand, Pizzolato and Reneger failed to observe any histological changes in rat sciatic nerves exposed to chloroprocaine and lidocaine for six hours.[12]

There have been several *in vivo* animal studies of the intrathecal administration of various local anaesthetics. Intrathecal 1 ml doses in dogs of a large number of local anaesthetics, including chloroprocaine, failed to produce any overt toxic effects.[13] However, the subarachnoid administration of large volumes of chloroprocaine in dogs resulted in paralysis of 35 per cent of treated animals.[14] Dogs treated with a similar volume of bupivacaine showed no paralysis. Moreover, the subarachnoid injection of saline at a pH of 3.0 was without effect.

TABLE II Summary of animal studies concerning potential neurotoxicity of 2-chloroprocaine and other local anaesthetics

Type of Study	*Investigator*	*Results*
Rabbit vagus nerve	Barsa	Local irritation with 2-CP, but not lido and bup
Rat sciatic nerve	Pizzolato	No irritation with 2-CP and lido
Spinal dog	Feldman	No toxicity with various LA
Spinal dog	Ravindran	Paralysis with 2-CP, but not with bup or low pH saline
Spinal rabbit	Wang	Paralysis with commercial 2-CP, and Na bisulfite, but not with pure 2-CP
Spinal sheep	Rosen	Minimal toxicity with 2-CP, lido, bup, and control solution
Spinal monkey	Rosen	Minimal toxicity with 2-CP and bup

2-CP = 2-chloroprocaine; bup = bupivacaine; lido = lidocaine.

In rabbits, commercial solutions of chloroprocaine caused paralysis when 16–20 mg were administered intrathecally, while preservative-free solutions of chloroprocaine failed to cause paralysis. Administration of sodium bisulfite, the antioxidant in commercial chloroprocaine solutions, also caused permanent paralysis in rabbits.[15]

An extensive study was conducted in sheep subjected to total spinal blockade with chloroprocaine, lidocaine or bupivacaine, or several control solutions.[16] Although signs of neurotoxicity were observed in some of the sheep, no clear differences in neurotoxicity were observed between the local anaesthetic solutions and the control solutions. Preliminary studies in eight monkeys failed to reveal any signs of paralysis following total spinal blockade with either chloroprocaine or bupivacaine. Histological evidence of demyelinization was observed in the spinal cord of several monkeys with both agents.[16]

In summary, the evidence accumulated to date in animals in an attempt to explain the prolonged sensory/motor deficit observed in several patients following subarachnoid administration of chloroprocaine is contradictory. While several studies have demonstrated neurological deficits following exposure to high doses of chloroprocaine, others

have failed to confirm these observations. One study has suggested that the neurological changes may be related to the anti-oxidant sodium bisulfite, present in the commercial solutions of chloroprocaine. Unfortunately, few of the studies have been published in detail sufficient to allow scientific scrutiny to detect possible reasons for the discrepancies. Moreover, studies which have been conducted in four different species may indicate a species difference in the susceptibility of neural tissue to local anaesthetics. The one factor that apparently has been ruled out is the pH of the chloroprocaine solution, since saline solutions of pH 3.0 have failed to produce neurological deficits. Additional careful studies are still warranted to clarify this controversy.

Until such time as additional evidence is accumulated, it would appear prudent to exert caution during the performance of epidural blocks and to utilize an adequate test dose, in order to avoid the accidental intrathecal administration of large doses of any local anaesthetic agent. Fractional doses of local anaesthetics probably should be injected, when possible, for epidural blocks. When large intrathecal doses of local anaesthetics have been administrated, the removal of approximately 10 ml of CSF and replacement with saline should be attempted in those situations where CSF aspiration is possible, although the efficacy of this procedure has not been established. Finally, there is little to be gained and much to be lost by frivolous charges and countercharges regarding the safety of chloroprocaine. There is no substitute for objective scientific data. Surely no one is interested in destroying unjustly a potentially useful agent or in defending unwisely a potentially toxic substance. Hopefully, we will not have to relearn the history of spinal anaesthesia in the United Kingdom where a generation of patients were deprived of this valuable anaesthetic technique due to concerns of neurotoxicity which were inadequately documented and studied. Since chloroprocaine has only recently been introduced in Canada, perhaps Canadian investigators can provide a more objective evaluation of the risk-benefit ratio of this particular agent.

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Neurotoxicité potentielle des agents anesthésiques locaux

L'agent anesthésique local 2-chloroprocaine (Nesacaine) a été récemment introduit au Canada alors qu'il était disponible aux Etats-Unis depuis plusieurs années. La chloroprocaine est un agent anesthésique local amino ester dont la structure est similaire à celle de la procaine. Son action est rapide et sa durée d'anesthésie relativement courte. Son avantage primordial en clinique est qu'il semble avoir moins de toxicité systémique à cause de son hydrolyse rapide par la cholinestérase du plasma. Récemment, la neurotoxicité potentielle de la chloroprocaine a été un sujet d'intérêt considérable aux Etats-Unis.

La neurotoxicité des agents anesthésiques locaux intéresse les anesthésistes depuis plusieurs années. Quoique des rapports sporadiques sur les réactions locales soient apparus dans des articles médicaux, d'amples études d'épidémiologie ont indiqué que l'emploi de l'anesthésie régionale est une procédure remarquablement inoffensive lorsqu'exécutée correctement.[1,2] Le plus grand intérêt concernant la neurotoxicité a trait à l'usage intra-dural des agents anesthésiques locaux puisque cet usage peut conduire à des effets catastrophiques produits par des lésions de la moëlle épinière chez un patient sain. Cependant des études sur l'épidémiologie de l'anesthésie rachidienne s'intéressant particulièrement à la tétracaine et à la lidocaine indiquent que cette technique est remarquablement sans danger.[3–5] Par contre il est connu que des agents anesthésiques locaux sont susceptibles de causer une irritation locale et une neurotoxicité atteignant des concentrations habituellement plus fortes que celles employées en clinique.[6]

L'intérêt porté au potentiel de neurotoxicité des anesthésiques locaux après l'administration intradurale a refait surface aux Etats-Unis suite à quatre cas de déficits sensoriel/moteur prolongés reliés semble-t-il à l'injection sous-arachnoidienne accidentelle de chloroprocaine.[7,8] Les éléments suivants nous ont obligés à porter notre attention sur ces quatre cas: 1) Chacun des quatre cas se présenta au cours d'un intervalle de six mois en 1979–1980. 2) Trois cas se présentèrent dans une institution en Indiana alors que le quatrième cas se présenta en Californie. 3) La plupart des cas semblent être à la suite d'injections intra-durales accidentelles de fortes doses de chloroprocaine qui étaient censées être employées pour l'administration dans l'espace épidural. 4) Toutes les patientes étaient des jeunes femmes en santé sans antécédents d'abnormalité neurologique. 5) Une similarité semble exister entre