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New Aspects in Regional Anesthesia 4

Major Conduction Block: Tachyphylaxis, Hypotension, and Opiates

Edited by
H. J. Wüst and M. d’Arcy Stanton-Hicks

With 31 Figures and 30 Tables

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Preface

Major conduction blocks utilizing local anesthetics or opiates are finding ever increasing applications in daily routine. However, two serious drawbacks are associated with their use: hypotension during surgery and the development of tolerance in long-term epidural analgesia. When opiates are injected epidurally or intrathecally, numerous side effects such as itching, nausea and vomiting, or respiratory depression have been reported.

The pathophysiology of complications arising during a major conduction block and measures to prevent them were discussed by 19 experts at the 4th International Symposium at Düsseldorf.

This volume contains 21 papers presented on three topics:

1. tachyphylaxis in long-term epidural anesthesia,
2. hypotension due to epidural and spinal anesthesia, and
3. effects and dangers of epidural and intrathecal opiates.

With regard to the safety of our patients during anesthesia, current practices of preventing complications were evaluated, and preliminary guidelines for a more rational approach toward prevention and treatment based on a knowledge of pathophysiologic mechanisms were developed. It is our hope that the anesthesiologist will profit from the discussion of regional anesthesia contained in this volume, many aspects of which have never before been presented in such detail.

Along with the three volumes previously published in this series, this book expands our knowledge of regional anesthesia. For the success of this symposium, we are indebted to the informative and very interesting contributions of both the speakers and the audience. In particular, we would like to acknowledge the generous support of Astra Chemicals, Germany, and Braun Melsungen, Germany.

This volume is dedicated to Professor Zindler on his 65th birthday in acknowledgement of his contributions to anesthetics in Germany.

Düsseldorf, March 1986

H. J. Wüst
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Chairmen: L. E. Mather and E. Hartung

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I Tachyphylaxis in Long-Term Epidural Analgesia

Chairmen: L. E. Mather and E. Hartung
Tachyphylaxis in Regional Anesthesia: Can We Reconcile Clinical Observations and Laboratory Measurements?

L. E. Mather

Introduction

Tachyphylaxis or acute tolerance is a nuisance phenomenon in “continuous” neural blockade. Anecdotal accounts of how it is produced or avoided in clinical practice are frequent but, in general, documentation is poor. In patients with pain, tachyphylaxis is manifested as either a diminished response to a standardized dose of local anesthetic or an increased dose requirement to maintain a consistent analgetic response. However, diminished response to the blockade of motor neurons may also be observed. To account for these observations, Tucker and Mather [1] proposed that either there is a true reduction in effect at the receptor level or the fraction of dose reaching the receptors decreases with successive injections.

It has been pointed out that tachyphylaxis is not an inevitable consequence of continuous neural blockade — it has been demonstrated neither convincingly nor reliably in animal laboratory studies [2]. It has even been stated that tachyphylaxis “occurs in some hands and not those of others” [2]. The purpose of this communication, therefore, is to consider the evidence for the occurrence of tachyphylaxis in regional anesthesia and to seek possible explanations. It is clear that the evidence needs to fulfill the criteria of both clinical and laboratory scrutiny.

The majority of clinically useful local anesthetic agents act through the combination of a selective mechanism and a nonspecific membrane expansion mechanism. Although they are deposited in the region where they act, the local anesthetic molecules must still diffuse through a series of barriers which impede the pathway to their target receptors located within an ordered membrane structure. At the same time, competition by blood flow seeking to remove these molecules to the general circulation and competition by temporary incorporation into other structures such as muscle and fat cells serves to reduce the fraction of dose ultimately available to combine with target receptors leading to neural blockade [3].

To account for tachyphylaxis, then, one must examine carefully the various processes involved in the production of neural blockade, starting with the nature of the solution injected, hence the milieu in which neural blockade occurs, and finally, the factors responsible for the termination of neural blockade (notably, systemic absorption).

Mechanisms of Tachyphylaxis

Bromage [4] noted that tachyphylaxis has been observed after both topical application and injection. It is most clearly recognized in association with central neural blockade, i.e., subarachnoid or epidural (both lumbar and thoracic). Because of the disparity between topical and central neural blockade, a unifying theory could seem to be extremely difficult to construct.
Renck [5] reviewed personal experience and available data and sought to summarize the knowledge concerning tachyphylaxis in epidural analgesia. He pointed out that the phenomenon occurs exclusively in intact animal and man. Since tachyphylaxis is not a property of isolated nerve systems, he concluded that it is unlikely that a diminished receptor level interaction is the cause. On the other hand, accumulating acidity is consistent with diminished access to receptors. Since Cohen and co-workers [6] demonstrated that the pH of dog cerebrospinal fluid decreased progressively with successive subarachnoid doses of local anesthetics, it has become customary to explain tachyphylaxis as a consequent progressive increase in the fraction of the ionized (conjugate acid) form of local anesthetic that has a diminished access to its receptor sites and produces diminished block. Others have verified that local pH is diminished by intraspinal injection of local anesthetic agents [7–9]. Depending on the quantity of the local anesthetic injected and the volume into which it is placed, the recovery of normal acidity may take from several minutes to several hours.

However, diminished response as a function of lower pH is not entirely supported by experimental studies. Adam [10] studied directly the effects of pH on sensory and motor nerve block in sheep. Subarachnoid injections of either 1.5% or 5% lidocaine at pH 4.5, or 6.5 containing 7.5% dextrose were studied. No differences in onset times due to pH were apparent. With 1.5% lidocaine, there was a tendency for the duration of sensory analgesia to be longer at the highest pH, but this trend was reversed with the 5% solution. Motor block induced by 5% lidocaine became consistently shorter with increasing pH. Even with peripheral nerves, the pH theory is not well-supported, since Reynolds et al. [11] found there were no significant differences in duration of action between aptocaine solutions at pH 5.6 and 6.8.

The observations that tachyphylaxis seems to occur more readily when shorter-acting agents are injected in larger doses and when longer-acting agents are injected in more concentrated solutions [5, 12] is consistent with the pH hypothesis. Both cases involve a larger injection of hydrochloric acid, which is the solubilizing acid. However, countering this argument is the observation by Bromage [4] that tachyphylaxis is minimized by injecting subsequent doses of the shorter-acting agents before analgesia regresses in the target segments. By minimizing the nonanalgesic interval the interval (between doses), this would lead to the maximum accumulation of acidity. By the same argument, carbon dioxide preparations of local anesthetic agent would be expected not to show tachyphylaxis resulting from acid accumulation. The fact that tachyphylaxis has been reported in the use of carbon dioxide-containing solutions of local anesthetic [13] is more evidence detrimental to the pH hypothesis.

Other suggestions put forward by Bromage [4] include the possibility of local vasodilatation at the injection site, causing progressively increased clearance of the local anesthetic from the injection site. Although it is difficult to be dogmatic on this point, studies in both patients [7, 14] and healthy volunteers [15] (Fig. 1) do not indicate excessive systemic concentrations of local anesthetic as compared with expected accumulation on the basis of pharmacokinetic characteristics of single-dose local anesthetic.

Figure 1 unequivocally demonstrates tachyphylaxis to lidocaine in a healthy young adult male volunteer. Repeated injections of 2% lidocaine HCl were made after recovery from the previous injection. Diminishing sensory blockade obtained by pin prick, as demonstrated by the decreasing areas of the time-segment diagrams, is classic evidence of tachyphylaxis affecting both spread and duration of blockade. In addition, sympathetic block, as revealed by the temperature of the great toe, eventually ceased, and at the same time, motor block was abolished [15].
Fig. 1. Composite diagram showing central venous plasma lidocaine concentrations, motor block (Bromage 0–3 scale), sensory block to pin prick, sympathetic block as revealed by the temperature of the great toe for a single subject (RP) receiving multiple epidural injections of 2% lidocaine plain. First injection was 20 cc (20L2), from which sensory block to C2 and motor block to C5–C6 were observed. After withdrawing the catheter 2 cm, subsequent injections of 10 cc (10L2) were made. Gray shaded areas indicate sensory blockade to pin prick. Numbers above or below the shaded areas indicate the approximate number of dermatom·min of sensory blockade per mg lidocaine injected. Dotted lines indicate area of hypalgesia to pin prick. (From [15])

A greater accumulation in the blood of the shorter-acting lidocaine (Fig. 1) than of the longer-acting etidocaine after repeated doses (Fig. 2) [15] is consistent with the predictions made by Tucker and Mather [1] on the basis of the greater fat solubility of etidocaine. It should be noted that lidocaine administered after repeated doses of etidocaine or bupivacaine...
still produces a respectable degree of blockade (Fig. 2). The reverse, however, is generally untrue [15]. One further point should be made concerning systemic absorption and the termination of local anesthetic action. It is possible that a feedback mechanism operates to decrease local anesthesia. Wüst and co-workers [16] reported that the onset of pain after a period of postoperative analgesia may be associated with increased mean arterial pressure and cardiac output. If this occurs in the interval between successive injections of local
anesthetic agent, then the heightened hemodynamic state may cause more rapid clearance of the local anesthetic agent into the general circulation [17], thereby diminishing the neural blockade.

Bromage [4] also suggested that local tissue reaction may cause an abnormal dispersion of the local anesthetic solution in the epidural space. While this may occur over a period of days in experimental animals, the time course of tachyphylaxis in man indicates that a time span of several hours would more appropriately characterize this reaction (Fig. 1). Furthermore, there is abundant clinical evidence that patients may be treated with continuous block procedures for weeks without either local reactions or tachyphylaxis. However, this concept has not been systematically evaluated in man.

Proposals for Future Investigations

Is there room for the advancement of new theories? A number of possibilities should be introduced, at least as starting points for new systematic investigations. First, the circadian nature of the duration of local anesthetic block should not be overlooked [18]. It has been observed that both skin wheals and peripheral nerve blocks are characterized by a circadian rhythm with a maximum duration at a daily time of approximately 3 p.m. It is possible that tachyphylaxis phenomenon represents a different rhythm with much longer phases.

Second, local anesthetic agents dispersed in lipid emulsions are less efficacious and less toxic than water solutions of the same strength [19]. This has been shown for two agents, lidocaine and quatacaine (a prilocaine derivative). Although the magnitude of the effects demonstrated was not large, they raise the possibility that the detergent-like action of local anesthetics may alter the structural integrity of the "epidural space", as suggested previously by Tucker and Mather [1]. This could affect the distribution characteristics of the local anesthetic agent as well as alter membrane permeability to electrolytes, thus giving rise to a progressively decreasing blockade.

Third, the role of hypernatriosis should not be overlooked as a factor promoting nerve irritability and conduction. Sodium ions are added to local anesthetic solutions to preserve isotonicity. Accordingly, higher concentrations of sodium ions are found in the more dilute solutions (Table 1). The potential for more dilute solutions to produce tachyphylaxis of

<table>
<thead>
<tr>
<th>Agent</th>
<th>Preparation</th>
<th>Sodium content (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine HCl</td>
<td>Xylocaine 0.5% plain</td>
<td>3.0–3.6</td>
</tr>
<tr>
<td>Lidocaine HCl + Adr.</td>
<td>Xylocaine 1% plain with Adrenaline 1:200000</td>
<td>2.2–2.8</td>
</tr>
<tr>
<td>Prilocaine HCl</td>
<td>Citanest 0.5% plain</td>
<td>2.9–3.5</td>
</tr>
<tr>
<td>Prilocaine HCl + Adr.</td>
<td>Citanest 2% plain with Adrenaline 1:200000</td>
<td>2.2–2.8</td>
</tr>
<tr>
<td>Bupivacaine HCl</td>
<td>Marcain 0.5% plain</td>
<td>2.8–3.5</td>
</tr>
<tr>
<td>Bupivacaine HCl + Adr.</td>
<td>Marcain 0.5% with Adrenaline 1:200000</td>
<td>3.0–3.6</td>
</tr>
<tr>
<td>Etidocaine HCl + Adr.</td>
<td>Duranest 1% with Adrenaline 1:200000</td>
<td>2.6–3.2</td>
</tr>
</tbody>
</table>
blockade would therefore be greater than for more concentrated solutions because the accumulation of sodium ions has a greater potential for locally reinforcing the need for more frequent injections. The role of concentration as a determinant of tachyphylaxis has not yet been adequately examined.

Fourth, the potential role of adenine nucleotides in established general and local anesthesia recently been emphasized [20]. All of the adenine nucleotides ATP, adenosine diphosphate (ADP), AMP, cyclic adenosine monophosphate (c-AMP), and the stable ester dibutyryl cyclic adenosine monophosphate (db-c-AMP) caused marked reductions in the duration of sciatic nerve block induced by procaine in rats [21]. Furthermore, they are capable of reversing established nerve blocks in isolated sciatic frog nerves. Thus, it could be hypothesized that, analogous to the effects of morphine, local anesthetics may initially inhibit the synthesis of c-AMP, thus permitting local anesthesia to be established. Subsequently, production rates could become reestablished during blockade, and even exceed preblock levels, thereby antagonizing subsequent injections of the local anesthetic. If any single hypothesis has the potential of becoming a unifying theory, then the antagonism of block by nucleotides must be considered one of the most important to date.

Despite incontestable evidence demonstrating the existence of tachyphylaxis, it must also be conceded that there is a wealth of clinical experience which appears to deny either the occurrence of tachyphylaxis or the attribution of obvious problems in patient management to tachyphylaxis. However, it should be noted that most of such clinical experience is derived from the long-acting local anesthetic agents etidocaine and bupivacaine. It should also be remembered that Tucker and Mather [1] suggested that the slower absorption characteristics of long-acting local anesthetic agents lead to local accumulation rather than accumulation in the blood upon repeated dosing (see also Fig. 1). This is a subtle form of tachyphylaxis that requires increasing amounts of agent locally to produce the same degree of block. Fig. 2 demonstrates this form of tachyphylaxis occurring at least in some segments. It is possible that tachyphylaxis from local anesthetic agents is an inevitable consequence of neural blockade — varying only in the method of appearance and the time course of onset and development.

The balance of evidence available suggests that a shift in emphasis from the study of physicochemical properties of the local anesthetic agent itself toward events occurring in the nerve during blockade should provide a stimulus for further research into this intriguing problem.

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