ANESTHESIOLOGY

When Regional Anesthesia Met Pharmacokinetics

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Pharmacokinetics of Local Anaesthetic Agents. By Tucker GT, Mather LE. Br J Anaesth 1975; 47(suppl 1):213–24

Abstract

Information derived from measurements of blood concentrations of local anaesthetics can be extended by the application of pharmacokinetic analysis. A better understanding of quantitative aspects of the disposition and absorption of these drugs should assist the anaesthetist in deciding the optimal agent and dosage for regional block techniques.

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It is an honor to represent our many colleagues who were involved in a collaborative research program on regional anesthesia from the late 1960s to the mid-1970s. This program, funded principally by the National Institutes of Health (Bethesda, Maryland), was performed in the Department of Anesthesiology at the University of Washington (Seattle, Washington) and its associated Anesthesia Research Center, and the Virginia Mason Hospital (Seattle, Washington) and its associated Research Center in Seattle, under the respective leaderships of John Bonica (1917 to 1994) and Dan Moore (1918 to 2015). After their experience with combat casualties from across the Pacific in World War II, Bonica and Moore established Seattle as a world-leading center of excellence for regional anesthesia. These legendary individuals progressively assembled a truly international group of clinicians and scientists to study regional anesthesia in depth. From the 1940s into the 1960s, their publications were mainly oriented toward the clinical performance and management of regional anesthesia and its complications. Our paper, chosen as a contribution to the Classic Papers Revisited series of this Journal, extends that clinical perspective and describes some of the more pharmacologic aspects of the regional anesthesia research performed at the University of Washington and its associated Anesthesia Research Center and the Virginia Mason Hospital and its associated Research Center some 50 yr ago.[1] A snapshot, taken in 1973, shows a typical research study of epidural anesthesia that contributed data to the chosen paper (fig. 1).

Our Colleagues

Our research group included anesthesiologists Mike Stanton-Hicks from Australia, Terry Murphy (1937 to 1996) from England, Peter Berges from Germany, and Bob Boas from New Zealand, together with brothers Phil Bridenbaugh (1932 to 2019) and Don Bridenbaugh (1923 to 2018), who were already associated with Dan Moore at the Mason Clinic. Allied programs at University of Washington and its associated Anesthesia Research Center were led by Ray Fink (1914 to 2000), Rudy de Jong (1928 to 2011), and Felix Freund (1918 to 2008), originally from England, The Netherlands, and Argentina, respectively. The authors, Laurie Mather and Geoff Tucker, are pharmacologic scientists from Australia and England, respectively.

From the late 1960s, the Bonica and Moore programs included studies of the amide-type local anesthetics lidocaine, mepivacaine, bupivacaine, and etidocaine. The long-acting agent bupivacaine, developed a decade earlier by the Swedish company Bofors AB (Nobelkrut, Sweden), was being introduced into the United States by Sterling-Winthrop, Inc. (Rensselaer, New York).[2] Etidocaine was being developed by the Astra Pharmaceutical Company (Worcester, Massachusetts) as a competing long-acting agent.[3] Our program also involved working with scientists at Astra, particularly Murray Blair, Jr. (1929 to 2010), Ben Covino (1930 to 1991), Jack Adams (1924 to 2017), Bertil Takman (1921 to 1996), Nick Boyes, and Helen Vassallo. This was an excellent model of academic–commercial research collaboration that generated solid intellectual content in addition to research funding.

Our Tasks

The time-course and quality of neural blockade after various procedures are, of course, the primary concerns in regional anesthesia. However, the rate of systemic uptake of the local anesthetic agent from the site of injection and its distribution in, and elimination from, the body are highly relevant to the risk of systemic toxicity (fig. 2). Such pharmacokinetic assessments require sensitive and specific measurement of drug concentration in the circulation. Phil Bromage (1920 to

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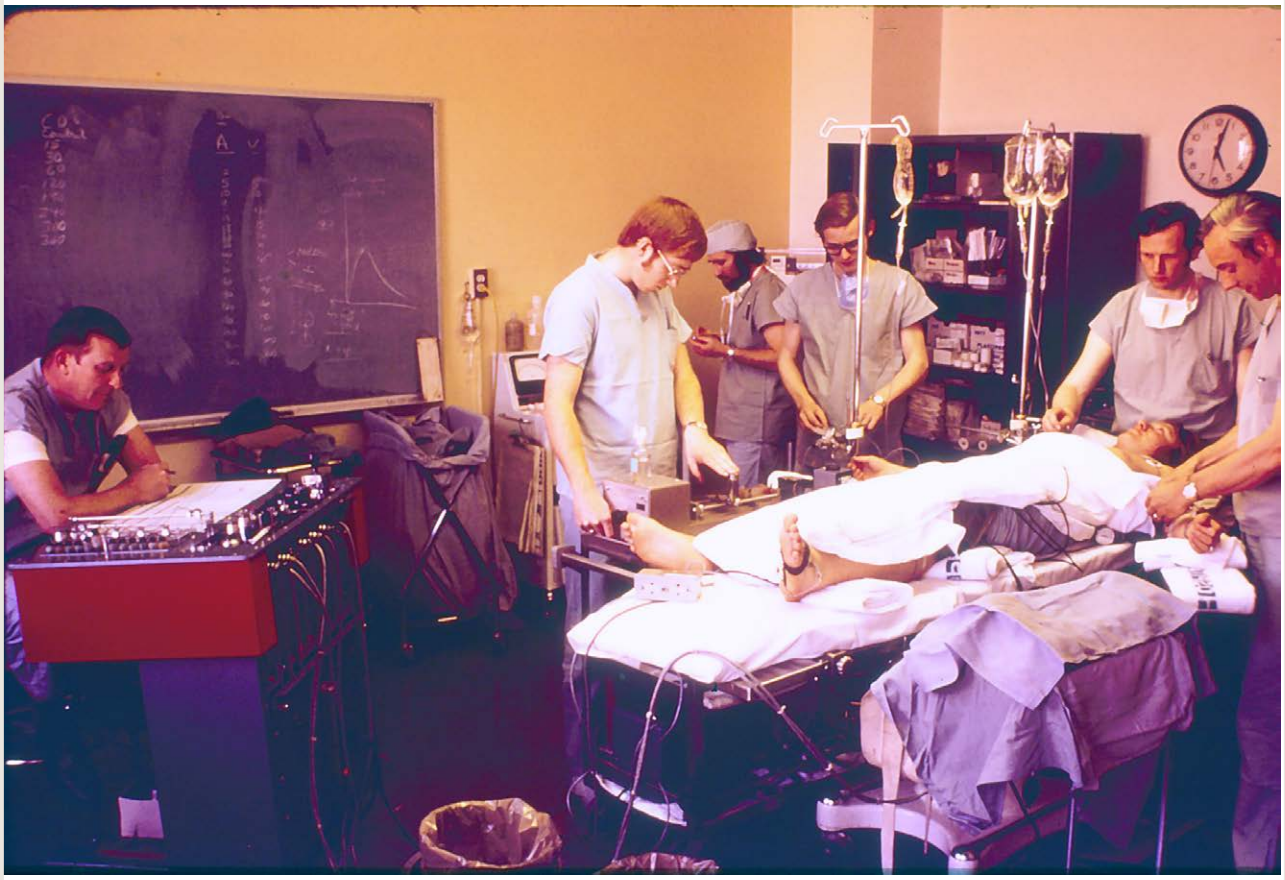

Fig. 1. A late-afternoon snapshot taken around 5 PM on another rainy day in Seattle in February 1973. The research team is performing a study in a disused operating room that had been converted into a human research laboratory at the Harborview Medical Center–King County Hospital, one of the main teaching hospitals of the University of Washington School of Medicine. The study was part of a program to determine the comparative neural and cardiovascular effects and pharmacokinetics of long-acting local anesthetics after epidural injection in healthy volunteer subjects. It had already been a long day in the laboratory, but the neural blockade was still solid, and the study still had some hours to go. Personnel (from *left*): Charles "Chuck" Pearcy (Anesthesia Research Center chief technician) monitoring the physiologic recorder, Gary Ledray (Anesthesia Research Center technician) measuring cardiac output by dye dilution, a bearded Laurie Mather measuring blood gases, Geoff Tucker sampling blood, Terry Murphy and Mike Stanton-Hicks assessing neural blockade, and a healthy volunteer patiently undergoing testing.

2014) in Montreal, Ontario, Canada, and Bruce Scott (1925 to 1998) in Edinburgh, Scotland, had previously reported plasma concentrations of local anesthetics from studies investigating differences between sites of injection, the tolerability of the agents, and the influence of added epinephrine.[5,6] The University of Washington and Virginia Mason Hospital research added new drugs, new techniques, and improved methodology, especially more rigorous analytical methods based on gas–liquid chromatography and innovative approaches to pharmacokinetic data analysis that did not become available until the mid-to-late 1960s.[7–13]

Our Paper

In September 1974, our paper, based on the pharmacokinetics of the four amide-type agents, was presented at a "Symposium on Local Anaesthetics" held in Edinburgh, Scotland. The program was organized under the headings of "The Chemistry and Physiology of Neural Blockade," "The Pharmacology and Clinical Evaluation of Local Anaesthetic Agents," and "Patient Management Under Neural Blockade." With similar numbers of international scientists and clinicians participating, the meeting was more of a small workshop than a typical anesthesiology symposium, with much frank discussion after each session. The symposium proceedings, including the discussions, were subsequently published as a supplement of the *British Journal of Anaesthesia*.

Our symposium paper compared pharmacokinetic properties of the longer-acting etidocaine and bupivacaine to the shorter-acting lidocaine and mepivacaine. We wrote about the importance of distinguishing between

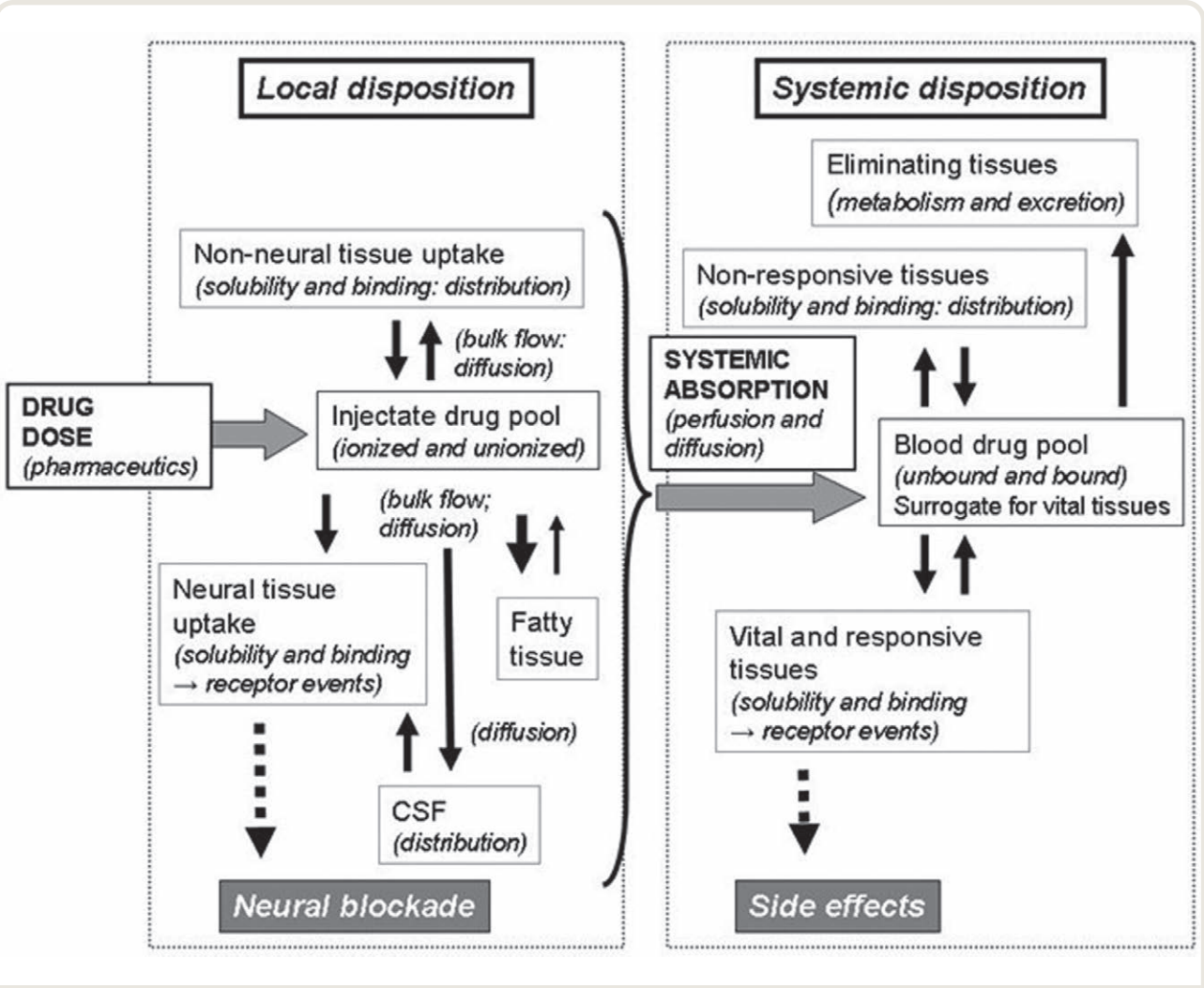

Fig. 2. A pharmacokinetic–pharmacodynamic model of the absorption and disposition of local anesthetics after epidural administration.[4] CSF, cerebrospinal fluid. From Mather LE, Tucker GT: Properties, absorption and disposition of local anesthetics, Neural Blockade, 4th edition. Edited by Cousins MJ, Bridenbaugh PO, Horlocker T, Carr DB. Philadelphia, Lippincott, 2008, pp 45–91. Reprinted with permission.

plasma and whole blood–drug concentrations, their different extents of binding to plasma proteins, and the need to define and assess unbound or free-drug concentrations in relation to effects. Our work also emphasized the relevance of arteriovenous drug concentration differences, especially in relation to systemic drug effects, an issue that is still not commonly appreciated. Also discussed were differences in systemic exposure after various block techniques with and without adjuvant epinephrine, disposition kinetics after intravenous injection, and the connection between pharmacokinetics and the hemodynamic effects of neural blockade. Quantitative estimates of the rates of systemic uptake from the site of injection after epidural injection and after cuff release with intravenous regional anesthesia were calculated by deconvolution of plasma drug concentration–time profiles after direct intravenous injection and after local injection. We concluded that the systemic pharmacokinetics of local anesthetic agents after epidural administration are dominated by the rate of absorption from the site of injection, rather than the rate of clearance from the body (a "flip-flop" model), with biphasic absorption patterns being due to the agents partitioning into the fatty milieu at the site of deposition, and with prolonged slower phases of absorption of the more lipophilic agents (fig. 2).

Our paper was the first systematic analysis of the pharmacokinetics of these agents. A 2004 survey ranked it 96th in the top 101 cited classics in anesthesia journals surveyed between 1945 and 1992, and it still gets cited occasionally.[14] Various other papers on drug analysis, neural blockade, and cardiovascular sequelae also came from our program.[15–21]

Our Program

As a background to the program, we faced an issue that was novel for most medical researchers and institutions at the time. Whereas the studies at Virginia Mason Hospital were performed on surgical patients, those at University of Washington used prisoner volunteers. Medical research involving prisoners was commonplace during the 1960s, especially in support of "phase I trials" required by the U.S. Food and Drug Administration. However, the ability of prisoner volunteers to provide "informed consent" came into question, highlighted in the early 1970s by several national scandals—although none involved the University of Washington—such that use of prisoners in medical research became prohibited.[22] With this project, we rapidly gained experience in writing proposals for a newly formed Institutional Review Board ("ethics committee") and preparing consent documents in lay language for healthy volunteer subjects.

As time progressed, etidocaine was discontinued as it produced a motor block that sometimes outlasted sensory block. Bupivacaine became, and remains, the *de facto* standard long-acting local anesthetic agent.

During the 1980s, it became more widely appreciated that many drugs that had been used for years were racemic mixtures of (typically two) chiral chemical compounds (enantiomers or stereoisomers) that might differ in pharmacologic and pharmacokinetic properties.[23] These compounds include diverse agents that the anesthesiologist knows well, including thiopental, isoflurane, methadone, propranolol, and ketamine.[24] Apart from lidocaine, which is achiral, the other principal amide local anesthetics—prilocaine, mepivacaine, and bupivacaine—were introduced as racemic mixtures. This simplified their chemical synthesis, and preclinical pharmacologic research performed in the 1950s and 1960s suggested that there were no adverse consequences of doing so. In the early 1970s, we were interested in investigating the enantioselective pharmacokinetics of the agents used as racemates, but the analytical technology at the time was incapable of separating stereoisomers; this technology would only become available in the late 1980s.[25,26]

In the 1990s, some pharmaceutical companies perceived the advantages of introducing appropriate enantiopure alternatives.[27] Among local anesthetic agents, ropivacaine, the enantiopure propyl homolog of S-bupivacaine, was launched at the 11th World Congress of Anaesthesiologists meeting held in Sydney, Australia, in 1996, and levobupivacaine, the S-enantiomer of bupivacaine, was launched at the European Society of Regional Anaesthesia meeting held in Gothenburg, Sweden in 2001. Both have been shown to exhibit an increment in safety over racemic bupivacaine.[28]

Fig. 3. The authors, Laurie Mather (*left*) and Geoff Tucker, at a Symposium on Intravenous Anesthesia held at the University of Cambridge (England) on March 28, 1988.

Our Contributions

Beyond publication of the 1974 symposium paper, we continued to collaborate and, among other things, wrote updated reviews of the pharmacokinetics of local anesthetic agents as new ideas and data became available.[4,29,30]

We each came to the Seattle anesthesiology research programs with expertise in the use of gas–liquid chromatography for drug analysis in biofluids and an understanding of the basic principles of pharmacokinetic modeling. Dr. Tucker had completed his Ph.D. research in 1968 (Department of Pharmacy, Chelsea College of Science and Technology, University of London, London, United Kingdom) under the supervision of the eminent medicinal chemist Arnold Beckett (1920 to 2010), with work that involved using gas–liquid chromatography in studies of the kinetics of absorption, metabolism, and excretion of various amphetamines, which, at that time, were widely used as doping agents in athletics. Dr. Mather had completed his Ph.D. in 1971 (Department of Pharmacy, University of Sydney, Sydney, Australia), under the supervision of the medicinal chemist Jack Thomas (1928 to 2017), with work that involved using gas–liquid chromatography in studies of placental transmission of lidocaine and bupivacaine when used in obstetric epidural anesthesia.

At the Third Asian and Australasian Congress of Anaesthesiology in Canberra, Australia, in 1970, John Bonica told Dr. Mather that he had read his work and offered him a job (!), adding that he thought that he and Dr. Tucker, who had already been recruited by Dan Moore, would work well together. This was indeed an accurate prediction: we have been colleagues and good friends now for more than 50 yr (fig. 3).

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Competing Interests

The authors declare no competing interests.

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