Factors Determining Dosages of Amide-type
Local Anesthetic Drugs

Daniel C. Moore, M.D.,* L. Donald Bridenbaugh, M.D.,† Gale E. Thompson, M.D.,‡
Robert I. Balfour, M.D.,§ William G. Horton, M.D.¶

The physical status of the patient (sex, age, weight, height, and underlying disease) has been thought to influence the dosage of local anesthetic drugs that can be injected without causing a systemic toxic reaction, but this belief is not supported by statistically significant data. Furthermore, previous studies of plasma levels of bupivacaine and mepivacaine showed no correlation between dosage and physical status, even when maximum dosages recommended by pharmaceutical companies were exceeded. This study of 9,287 regional blocks, using the statistical tests of multiple regression and chi square, substantiates that the occurrence of systemic toxic reactions in adults does not correlate with dosages and/or physical status of the patient when 400 mg or less of bupivacaine, 450 mg or less of etidocaine, or 500 mg or less of mepivacaine is used. Therefore, the study questions the maximum dosages established for certain local anesthetic drugs, as well as the method by which such dosages were established. (Key words: Anesthesia, local, bupivacaine; Anesthetics, local, etidocaine; Anesthetics, local, mepivacaine; Toxicity, local anesthetic drugs.)

MOST, if not all, systemic toxic reactions from amide-type local anesthetic drugs are the result of high blood levels of the drugs. Plasma level determinations of such drugs after regional block procedures have confirmed that: 1) using the same volume and concentration, the rate of absorption varies depending on the site of injection; 2) the higher the concentration and/or the milligram dose, the greater the blood level of the anesthetic drug; 3) a solution containing epinephrine, compared with the same solution without epinephrine, results in a lower blood level of the local anesthetic drug.[1–5]

In addition to these known factors, the physical status of the patient (age, weight, height, sex, and underlying disease) has been thought to influence the blood level of the local anesthetic agent and, by extension, the maximum dosages.[6–9] As a result, maximum dosages are usually based not only on weight but also on other factors in the physical status of the patient.[10] However, no statistically significant data have been obtained to support this contention. On the contrary, arterial and venous plasma studies in 50 adult patients who received injections of bupivacaine (Marcaine, Winthrop) with epinephrine, 150 or 225 mg, for epidural block, 300 mg for brachial plexus block, and 400 mg for bilateral intercostal nerve block or for sciatic femoral nerve block showed no correlation between criterion values (peak arterial plasma levels, time to peak arterial plasma levels, peak venous plasma levels, and time to peak venous plasma levels) and predictor values (dosage, sex, age, height, weight, and physical status).[4,5] Also, a study of 70 adult patients who received mepivacaine (Carbocaine, Winthrop) 500 mg, with and without epinephrine, for caudal, epidural, bilateral intercostal nerve, brachial plexus, or sciatic nerve with femoral nerve block, showed no correlation between weight, dosage, and arterial and venous plasma levels.[3]

Therefore, a study was designed to investigate the total milligram dosages (volumes and concentrations) of the amide local anesthetic drugs that we use for specific regional block techniques, and to relate these dosages to the patients' physical status (sex, age, weight, height, and underlying disease). Moreover, patients who had generalized systemic toxic reactions were further investigated to determine the relationship of the milligram dose to their physical status.

Method of Study

Since July 1967 we have employed a computer-oriented anesthetic record to collect anesthetic data and for research.[11,12] The prospective data from this record are stored on computer tapes, and the anesthetic record itself is microfilmed before it is destroyed. A computer review of these tapes from July 1967 through June 1976 provided the data for this study, and a reproduction of the microfilms of those patients who had generalized systemic toxic reactions provided close scrutiny of the notes on the anesthetic record as well as the grid containing blood pressure, pulse, respiratory rate, etc.

* Senior Consultant in Anesthesiology, The Mason Clinic and The Virginia Mason Hospital, and Clinical Professor of Anesthesiology, Department of Anesthesiology, University of Washington School of Medicine, Seattle, Washington.

† Director, Department of Anesthesiology, The Mason Clinic, and Clinical Professor of Anesthesiology, University of Washington School of Medicine.

‡ Staff Anesthesiologist, The Mason Clinic, and Clinical Assistant Professor of Anesthesiology, University of Washington School of Medicine.

§ Staff Anesthesiologist, The Mason Clinic, and Clinical Instructor of Anesthesiology, University of Washington School of Medicine.

¶ Staff Anesthesiologist, The Mason Clinic, and Clinical Associate Professor of Anesthesiology, University of Washington School of Medicine.

TABLE 1. Multiple-regression Values

	Number of Cases	Dose (mg) Mean ± SD	Sex (Per Cent Males)	Age (Years) Mean ± SD	Weight (Pounds) Mean ± SD	Height (Inches) Mean ± SD	Physical Status Per Cent of Patients					Coefficient of Determination (Per Cent)
							1	2	3	4	5	
Surgery												
Bupivacaine (epinephrine)												
Epidural	1,814	139 ± 22	8	42 ± 13	143 ± 28	65 ± 3	74	23	2	0	0	4.4
Brachial plexus	405	219 ± 79	56	50 ± 17	159 ± 37	67 ± 4	56	35	9	1	0	4.0
Sciatic, femoral, etc.	349	269 ± 94	51	45 ± 18	160 ± 37	67 ± 4	60	33	7	0	0	4.3
Intercostal (bilateral)	911	266 ± 76	44	59 ± 15	148 ± 33	66 ± 4	21	49	25	4	0	1.1
Intercostal (bilateral) with celiac plexus	249	332 ± 80	40	47 ± 13	153 ± 31	66 ± 4	58	35	6	1	0	6.1
Etidocaine (epinephrine)												
Epidural	357	190 ± 36	6	44 ± 12	143 ± 25	64 ± 3	73	25	2	0	0	4.9
Intercostal (bilateral)	446	278 ± 71	55	60 ± 12	153 ± 32	66 ± 4	23	43	31	3	0	2.4
Diagnostic and therapeutic												
Bupivacaine (epinephrine)												
Intercostal	351	183 ± 75	59	56 ± 14	152 ± 33	67 ± 4	33	40	25	1	0	2.8
Obstetrics												
Bupivacaine (epinephrine)												
Caudal												
Single-dose*	1,091	103 ± 24	0	26 ± 5	159 ± 27	64 ± 3	90	9	0	0	0	3.1
Intermittent-dose†	455	0.75/min ± 0.61	0	26 ± 5	161 ± 29	65 ± 3	90	10	0	0	0	1.4
Epidural	322	103 ± 34	0	25 ± 5	153 ± 22	64 ± 2	96	4	0	0	0	2.7
Bupivacaine (plain)												
Caudal, single-dose*	342	97 ± 37	0	26 ± 5	155 ± 26	65 ± 3	86	13	1	0	0	0.7
Mepivacaine (epinephrine)												
Caudal (intermittent)†	1,581	2.60/min ± 1.49	0	25 ± 5	155 ± 25	65 ± 3	96	4	0	0	0	1.4
Mepivacaine (plain)												
Caudal (intermittent)†	614	3.24/min ± 1.82	0	25 ± 5	153 ± 22	65 ± 3	96	4	0	0	0	2.8

* Plastic tubing inserted but only the initial dose was necessary.

† At the start of this study, it was thought that the only way to calculate dosage for an intermittent technique, should absorption result in a systemic toxic reaction after a reinforcing (refill) dose, was on the basis of drug per minute. However, no such reaction occurred.

Each group of regional blocks to be included in this study required a minimum of 200 blocks performed with the same amide local anesthetic drug. In addition, all the variables to be reviewed must have been coded on the anesthetic record. The groups were divided according to whether the block was administered for a surgical, obstetric, diagnostic, or therapeutic procedure, and whether the solution contained epinephrine. Compounded solutions—*e.g.*, mepivacaine plus tetracaine (Pontocaine, Winthrop)—were excluded.

To assess the relationship between the set of predictor variables (sex, age, weight, height, and underlying disease) and the criterion variable (milligram dosage of the local anesthetic agent), we selected the statistical procedure of multiple regression. For intermittent-dose techniques, the dosage per minute was used as the criterion value. Of the set of predictor variables, age, weight, sex and height were used directly. The coding for physical status used the American Society of Anesthesiologists rating system: 1 = normal healthy patient; 2 = patient with a mild systemic disease; 3 = patient with a severe systemic disease that limits activity but is not incapacitating;

4 = patient with an incapacitating systemic disease that is a constant threat to life; 5 = moribund patient not expected to survive 24 hours with or without surgery.[13]

In order to evaluate the incidence of generalized systemic toxic reactions in the patient population, we identified the multiple-regression values of the predictor variables and of the criterion dose for each individual who experienced such a reaction. A chi-square value relation to the degree of similarity between their cases and the mean values obtained from the multiple-regression study was calculated. The data were analyzed by computer.

Results

Of the amide local anesthetic drugs that we employ for regional block techniques, only bupivacaine, etidocaine (Duranest, Astra), and mepivacaine fit the criteria of this study. Of the 12,313 blocks done with these drugs, 9,287 met the parametric requirements of the study, and they were arranged in 14 groups, ranging from 249 to 1,814 blocks (table 1).

The statistical procedure of multiple regression showed that the dosage levels administered to patients

in the 14 categories were independent of considera-tion of patient sex, age, weight, height or physical status (table 1). The coefficients of determination ranged from 0.7 to 6.1 per cent. This indicates that in all cases a trivial amount of variation in the dosages is accounted for by the set of predictor variables. This would suggest that, although there appears to be a systematic relationship between one or more predictors and the criterion, it is very small and consequently unimportant.

In nine of the 9,287 patients (0.1 per cent), inad-vertent intravascular bolus dose injections of a local anesthetic solution occurred—six with bupivacaine, one with etidocaine, and two with mepivacaine (table 2). Of the nine patients, eight showed evidence of systemic toxic reactions. Seven patients convulsed, one who received bupivacaine had tinnitus only, and one who received bupivacaine showed no evidence of

a reaction. The reactions followed either attempted single-dose epidural (peridural) block (three patients) or the initial dose of an intermittent (continuous)-dose technique (five patients). The convulsions were treated immediately and correctly with no untoward sequelae.

None of these patients had any evidence of anes-thesia from the regional block technique. Further-more, in the six patients in whom the anesthetic drug had been injected through a catheter, blood was obtained by aspiration after the convulsion, although when this test was done following the initial placement of the tubing, none could be aspirated. Three of the patients were scheduled for surgical procedures, and none of the procedures was canceled. One patient received general anesthesia; one, spinal block with tetracaine–dextrose solution; in the other the epidural block was repeated with the same drug. Of

TABLE 2. Characteristics of Patients Having Intravascular Injections of the Amide Local Anesthetic Agents

	Dose (mg)	Concentration (Per Cent)	Age (Years)	Weight (Pounds)	Height (Inches)	Physical Status (ASA Scoring)	Type of Reaction	Degree of Anesthesia	Type of Anesthesia and Dosage for Surgical and Obstetrical Procedures
Surgery									
Bupivacaine (epinephrine)									
Epidural									
* 1. Vaginal hysterectomy	135	0.75	43	133	66	2	Convulsion	None	General anesthesia
2. Abdominal hysterectomy	75	0.75	59	165	68	1	Convulsion	None	Spinal block (tetracaine)
Etidocaine (epinephrine)									
Epidural									
3. Vaginal hysterectomy	100	1.0	49	140	62	1	Convulsion	None	Needle replaced (epidural space), 18 ml of 1.0 per cent etidocaine injected‡
Obstetrics									
Bupivacaine (epinephrine)									
Caudal, initial dose of inter-mittent (continuous)-dose technique									
4. Vaginal delivery	44	0.25	24	158	65	1	No reaction	None	Plastic tubing replaced (caudal canal), 17 ml of 0.25 per cent bupivacaine injected‡
5. Vaginal delivery	100	0.5	28	170	62	1	Convulsion	None	Spinal block (tetracaine)
6. Vaginal delivery	100	0.5	22	131	67	1	Convulsion	None	Pudendal block (lidocaine)
7. Vaginal delivery	50	0.25	27	155	63	1	Tinnitus	None	Plastic tubing pulled back, 20 ml of 0.25 per cent bu-pivacaine injected‡
Mepivacaine (epinephrine)									
Caudal, initial dose of inter-mittent (continuous)-dose technique									
8. Vaginal delivery	230	1.0	31	147	65	1	Convulsion	None	Plastic tubing replaced (caudal canal), two doses of 22 ml of 1.0 per cent mepivacaine = 440 mg‡
9. Vaginal delivery	190	1.0	21	146	61	1	Convulsion	None	Plastic replaced (caudal canal), two doses of 18 ml of 1.0 per cent mepivacaine = 360 mg‡

* Each number represents a patient.
† Solution contained epinephrine, 1:200,000.

the six parturients in whom intermittent-dose techniques were attempted, two who convulsed were ready to deliver by the time they recovered from the reaction—that is, they appeared to be rational and to have recall following the reaction. One received a pudendal block with lidocaine (Xylocaine, Astra), while the other had a spinal block with tetracaine–dextrose. In the other four parturients, the catheter was pulled back slightly or removed and reinserted, and the block established with the same agent (table 2). Whenever possible, the same drug and dosage were employed for the repeat of the regional block to eliminate the possibility that rapid absorption or allergy caused the reaction.

Inspection of the characteristics of each patient who convulsed indicates no relationship with the local anesthetic solution, with the procedure (surgical, obstetric, diagnostic, or therapeutic), with site of administration of the anesthetic solution, or with the method of administration—*i.e.*, single or intermittent dose. In all cases the anesthetic solutions were administered with epinephrine. However, in other categories the anesthetic solutions were also administered with epinephrine, and systemic toxic reactions occurred. Except for one patient, the individuals who experienced systemic toxic reactions did not differ from those who experienced no reaction. This patient (number 2, table 2), whose physical status was 1, varied from the mean as follows: 1) the dose resulting in the reaction was 75 mg, compared with a mean of 139 mg; 2) her age was 59 years and the mean was 42 years; 3) her weight was 115 pounds (52.3 kg) and the mean was 143 pounds (65 kg); 4) her height was 61 inches (152.5 cm) and the mean was 65 inches (162.5 cm). The principal difference was that the milligram dosage of bupivacaine was significantly less than the mean.

Discussion

Systemic toxic reactions do occur as a result of absorption. However, such reactions are minimal compared with those resulting from intravascular injection. In none of the 9,287 patients in this study did systemic toxic reactions occur from absorption. All such reactions followed inadvertent intravascular bolus doses of the local anesthetic, and they occurred even though routine tests for blood performed prior to injecting the local anesthetic drug were negative. They occurred during single- or intermittent- dose caudal or epidural blocks because the bevel of a needle or the opening in catheter had been inadvertently placed intravascularly. Regardless of the patient's physical status or the drug, a large bolus dose usually

results in convulsions (table 2). Experiences of Lund *et al.* confirm our findings that the incidence of systemic toxic reactions is small and that they usually occur after intravascular injection rather than absorption. Following 2,206 blocks (epidural 1,257, caudal 174, brachial plexus 280, and miscellaneous 495), they found two systemic toxic reactions progressing to convulsions (0.1 per cent) resulting from intravascular injections during attempts to perform epidural blocks with etidocaine, and none resulting from absorption.[14]

Maximum recommended dosages of local anesthetic drugs are stated most often in milligrams per kilogram or pounds and/or milligrams per regional block technique.[14] Such doses are usually determined by: 1) extrapolating data obtained by research in laboratory animals to man; 2) clinical investigations in man using these extrapolated doses for peripheral nerve and epidural block anesthesia. When this method of studying local anesthetic drugs is used to determine what is *believed* to be the maximum milligram dosages for man, and these dosages are then published in packaged inserts and the *Physicians' Desk Reference*, an unfortunate situation develops, for the following reasons.[10] First, the extrapolated data are based only on the weight of the animal and its relationship to the *absorption* of the local anesthetic drug, usually from the peritoneal cavity of the animal. Second, data obtained from *absorption* from the peritoneal cavity of the animals has little, if any, relationship to regional block techniques done in man, which seldom, except for peritoneal lavage, would be comparable.[7] Third, a single maximum dose is stated for all regional block techniques when it is known that absorption of local anesthetic solutions varies according to the site of injection, whether they contain epinephrine, and what concentration and volume (total milligram dose) is used.[1] Fourth, dosage based only on weight often limits unjustly the use of local anesthetic drugs for certain regional blocks, particularly extensive peripheral nerve blocks—*e.g.*, bilateral block of the sixth through the twelfth intercostal nerves combined with celiac plexus block. When dosage is based on weight and the patient is small, the total milligram dose, *believed* to be the maximum safe amount of the local anesthetic drug, may not permit the use of a concentration and volume adequate to produce the required sensory and/or motor blockade. Fifth, the number of generalized systemic toxic reactions that occur following regional block techniques from either absorption or intravascular injections is minimal, provided that the dosages we employ are not exceeded. The number of systemic toxic reactions from *absorption* following

caudal, epidural, or peripheral nerve block is small, if not infinitesimal. In 9,287 patients, none occurred. Such reactions are more likely to occur as a result of a large inadvertent intravascular bolus injection following caudal or epidural block, where the position of the needle or plastic tubing is not changed during injection, rather than a peripheral nerve block, where the needle is seldom fixed in one position. In the 9,287 patients, there were eight such unpreventable reactions (0.09 per cent). Sixth, the intravascular bolus doses that produce convulsions are usually significantly less than the maximum doses of local anesthetic agents recommended by pharmaceutical companies on the basis of absorption data. Therefore, using the maximum stated dose or less does not guarantee that a systemic toxic reaction will not occur, or if it does occur, that its severity will be less or that it will be easier to treat. Seventh, after the drug is marketed, it is usually found to be much safer in man than the data obtained by extrapolation, etc., indicate. Eighth, the packaged inserts often state conservative maximal doses, either to get approval from government regulating agencies or to avoid medicolegal action should a complication occur. Finally, once such doses have been accepted by a government regulatory agency, they are difficult to change, even if proven wrong by animal research, human research, or both.

Conclusions

Maximum doses of local anesthetic drugs and reduction of these doses in the patient with a poor physical status, as stated by pharmaceutical companies based on extrapolation of animal data and limited clinical investigation, are open to question. They restrict the use of some regional block techniques that require large milligram doses of local anesthetic drugs, particularly peripheral nerve block in the patient with an ASA physical status or 1 and 2. Even more important, they eliminate completely the use of many regional block techniques in the patient with an ASA physical status of 3, 4, and 5 when these techniques would be the anesthetic procedure of choice.

For single-dose caudal and epidural blocks in adult patients, regardless of sex, age, weight, height, and underlying disease, the following dosages have been used safely by us: 1) bupivacaine, 0.25, 0.5, and 0.75 per cent, with epinephrine, 1:200,000, and 225 mg or less; 2) etidocaine, 0.5, 1.0, and 1.5 per cent, with epinephrine, 1:200,000, and 450 mg or less; 3) mepivacaine, 1.0, 1.5, and 2.0 per cent, with epinephrine, 1:200,000, and 500 mg or less.

For single-dose peripheral nerve blocks in adult patients, regardless of sex, weight, height, and underlying disease, the following dosages have been used safely by us: 1) bupivacaine, 0.25 and 0.5 per cent, to 400 mg or less, with epinephrine, 1:200,000, or less; 2) etidocaine, 0.5 per cent, to 450 mg or less, with epinephrine 1:200,000, or less; 3) mepivacaine, 1.0 per cent, to 500 mg or less, with epinephrine, 1:200,000, or less.

While these doses are adequate for performing any epidural, caudal or peripheral nerve block, such doses are not used in all instances. As regional block techniques are mastered, volumes and thus total milligram doses smaller than these may produce satisfactory results. When they do, then such smaller doses should be used. However, when a regional block technique is being learned, the beginner may use these doses when necessary, for they will increase his incidence of success. It should be cautioned that when the analgesia after the initial block from the above-stated doses is unsatisfactory, the safety of repeating such a dose cannot be attested to by us. Furthermore, when doses significantly larger than these are injected, it is quite likely that a relationship of them to physical status and the incidence of systemic toxic reactions might emerge.

While systemic toxic reactions from absorption or inadvertent intravascular injections of local anesthetic drugs occur infrequently—in this study, eight in 9,287 patients (0.09 per cent)—it behooves the physician employing these drugs to use them correctly and to be able to recognize such a reaction immediately and treat it correctly. *Unfortunately, all too often, when a systemic toxic reaction occurs, attention is focused on the dosage of the local anesthetic drug, rather than on the ability of the physician employing the drug.*

Finally, although animal data are the essential first step in the study of any drug, the validity of extrapolating such data to man has yet to be proven conclusively. If we are to avoid establishing restrictive doses of a valuable drug and thereby limit its use in man, a standard protocol must be developed for more extensive evaluation of drugs in man. To quote Lasagna, "Modern drug evaluations . . . are remarkably artificial in the sense of not resembling the real-life application of medicaments. . . . The therapeutic 'action' (to use the American jargon) is at the hospital bedside and in the home of the sick patient; it is there that drugs ought to stand or fall by their performance. It is high time that we stopped trying to comment on drug performance without data of sufficient quality to justify professional regulatory assessment and decisions."[15]

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