5

Pharmacokinetic Aspects of Local Anesthetic Agents

Local anesthetic agents are applied directly to the region of the body in which they exert their desired pharmacological action, whereas other therapeutic agents usually are administered either parenterally or orally and then transported by the circulatory system to their target organ, located at some distance from the site of administration. Local anesthetic activity and, particularly, the toxicity of this class of drugs are influenced by factors such as systemic absorption from site of injection, distribution, metabolism, and excretion. Due in large part to the development of specific and sensitive analytical methods, such as gas chromatography, for measuring the concentration of local anesthetic drugs in blood and urine, a considerable body of information is presently available concerning the physiological disposition of local anesthetic agents.

ABSORPTION

The most important determinants of absorption are (a) the site of injection, (b) the dosage of local anesthetic agent administered, (c) the addition of a vasoconstrictor agent to the local anesthetic solution, and (d) the pharmacological profile of the local anesthetic drug itself (Table 31).[143,189,212]

Site of Injection

The blood levels of different local anesthetic agents have been measured following their administration into various anatomical sites. In general, a consistent pattern of vascular absorption exists regard-

Table 31

FACTORS INFLUENCING ABSORPTION OF LOCAL ANESTHETIC AGENTS

1. SITE OF INJECTION
2. DOSAGE
3. ADDITION OF A VASOCONSTRICTOR AGENT
4. PHARMACOLOGICAL CHARACTERISTICS OF DRUG

less of the anesthetic agent employed; namely, (a) the highest anesthetic blood level is obtained following intercostal nerve blockade,[143, 189, 212] (b) the maximum concentration of local analgesic agent in blood decreases according to the site of administration in the following order: caudal canal, lumbar epidural space, brachial plexus region, and sciatic-femoral region,[143, 189, 200, 212] (c) the lowest anesthetic blood levels have been observed following subcutaneous administration of local anesthetic agents for infiltration anesthesia[143, 252] (Fig. 5-1). This general pattern of systemic absorption from various sites of administration has been demonstrated for lidocaine, prilocaine, mepivacaine, and etidocaine[143,185,189,212] (Fig. 5-1). The fact that anesthetic blood levels differ following administration into different anatomical sites is related to a multiplicity of factors. The high blood concentration observed following intercostal nerve blockade is probably attributable to the multiple injections required for this peripheral nerve-blocking procedure such that the local anesthetic solution is exposed to a larger vascular surface area, which results in a greater rate and degree of absorption. The higher anesthetic blood levels obtained following caudal anesthesia as compared to lumbar epidural administration may reflect the greater vascularity of the bony tissue in the caudal canal, which could promote the systemic absorption of local anesthetic agents from that site.[253] In addition, there are relatively large amounts of adipose tissue in the lumbar epidural space, which could serve as a depot site for local anesthetic agents, thereby tending to retard vascular absorption.[200, 212] An interesting study comparing anesthetic blood levels following different modes of administration was conducted by Mazze and Dunbar.[161] The venous blood levels of lidocaine were determined after brachial plexus blockade and intravenous regional anesthesia to evaluate the relative safety of these regional anesthetic techniques for certain surgical procedures involving the upper limb. A significantly lower

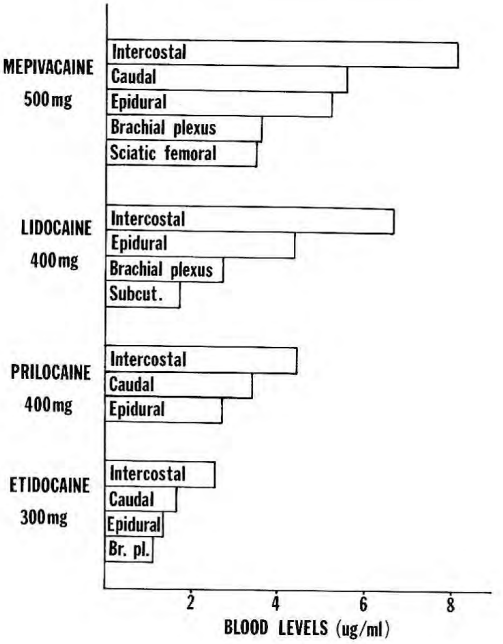


Fig. 5-1. Comparative peak blood levels of several local anesthetic agents following administration into various anatomical sites.

venous blood level of lidocaine was observed following tourniquet release in the intravenous regional procedure (1.5 ± 0.2 μg/ml) as compared to the peak lidocaine blood level after brachial plexus blockade (2.5 ± 0.5 μg/ml). This relationship of administration site to rate of drug absorption has obvious clinical significance, since the same dose of a local anesthetic agent may be potentially toxic in one injection area, but not in others. For example, average peak blood levels in excess of 6 μg/ml have been reported with the use of 400 to 500 mg of lidocaine and mepivacaine for intercostal nerve blockade, as compared to average peak blood levels of 4–5 μg/ml when the same dose of these two drugs was employed for lumbar epidural anesthesia.[143, 189] Since the frequency of adverse events is greater when the blood level of lidocaine and mepivacaine exceeds 5 μg/ml, the results of these studies would indicate that the potential for systemic local anesthetic toxicity is significantly greater following intercostal nerve blockade than after lumbar epidural anesthesia, despite the use of the same total dose of local anesthetic agent for both procedures.

Absorption of local anesthetic agents is affected not only by

administration into markedly different anatomical sites, but also by injection into different muscle masses (Fig. 5-2). A significantly higher peak blood level has been observed to occur following administration of lidocaine into the deltoid muscle as compared to injection into the vastus lateralis and gluteus maximus.[254–256] The greater absorption from the deltoid muscle appears related to the greater blood flow in that particular muscle mass than in the vastus lateralis.[257] The extremely low levels of lidocaine following injection into the gluteus maximus may reflect the greater adiposity in this region which could serve as a depot site for the local anesthetic agent and so retard its vascular absorption. Again, this variation in absorption from different muscle sites has practical clinical applicability. In this particular situation, the use of different muscle sites has therapeutic rather than toxic implications when a drug such as lidocaine is used for antiarrhythmic purposes. Thus, 200–300 mg of lidocaine injected into the deltoid muscle produces a blood level in excess of 2 μg/ml, which is normally considered to be adequate for antiarrhythmic activity. This same dose of lidocaine injected into the gluteus maximus or vastus lateralis results in a peak venous blood level of less than 2 μg/ml, which is usually inadequate for antiarrhythmic therapy[256] (Fig. 5-3).

The topical application of local anesthetic agents at various sites also results in differences in absorption and toxicity[124] (Fig. 5-4). In general, the rate of absorption of local anesthetic agents occurs most rapidly following intratracheal administration. The relative absorption

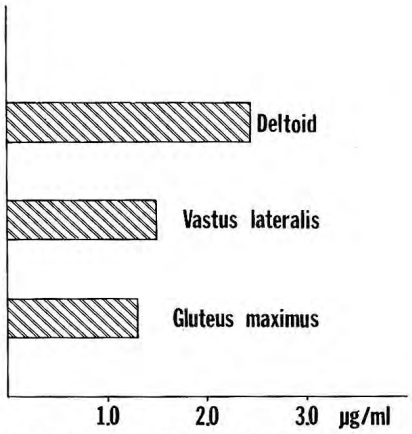


Fig. 5-2. Peak venous plasma levels of lidocaine following administration into different muscle sites.

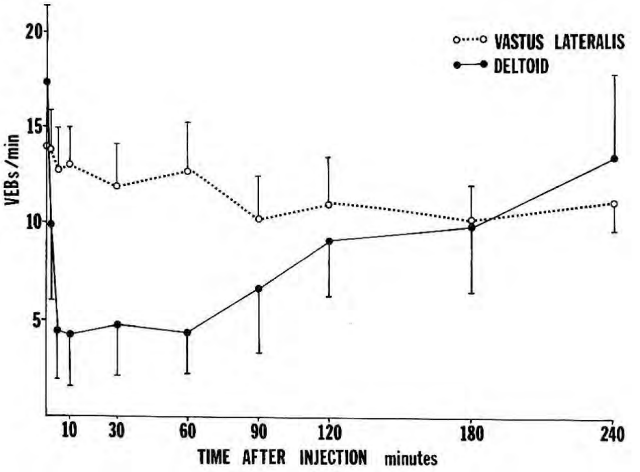


Fig. 5-3. Frequency of ventricular extrasystoles (VEB) following intramuscular administration of 300 mg lidocaine into the deltoid or vastus lateralis muscle.

and toxicity of local anesthetic agents is less following intranasal instillation and administration into the urethra and urinary bladder. Extremely low levels of lidocaine have been observed following the oral administration of this agent.[258, 259] These differences in absorption from various sites of topical application are due, in part, to the inherent variations in vascularity of the different anatomical sites and to the differences in pharmaceutical anesthetic preparations utilized

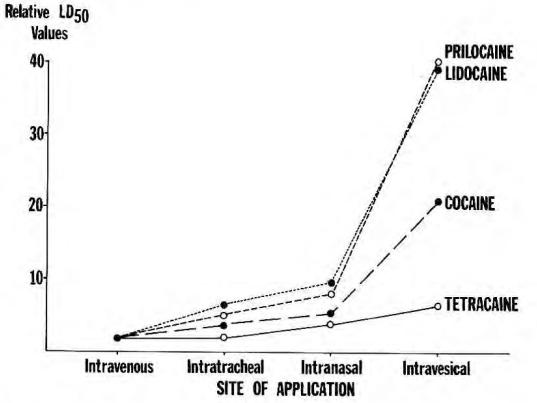


Fig. 5-4. Comparative toxicity of several local anesthetic agents as related to site of topical application.

for different forms of topical anesthesia. For example, the rapid absorption from the tracheobronchial tree is undoubtedly related not only to the vascularity of this area, but also to the use of anesthetic sprays which tend to disperse the anesthetic solution over a wide surface area and thus promote vascular absorption. On the other hand, local anesthetic agents are commonly employed in an ointment or gel form when applied to mucous membranes or instilled into the urethra. This formulation would tend to delay vascular absorption. The extremely low levels of lidocaine observed following oral administration may be due, in part, to a poor absorption from the gastrointestinal tract, but probably is more related to the rapid degradation of this agent as it is absorbed from the gastrointestinal tract and passes through the liver.[258, 259] For this reason, lidocaine, which is an effective antiarrhythmic drug when administered intravenously, is of little value orally in the treatment of cardiac arrhythmias.

Not only do local anesthetic agents vary in their absorption rates from various sites of topical application, but differences also exist between individual local anesthetic agents with regard to their relative absorption from specific sites. The toxicity of tetracaine following intratracheal instillation is similar to its intravenous toxicity, which suggests an extremely rapid rate of absorption following its administration into this particular site[124] (Fig. 5-4). Absorption from this particular site is apparently not so rapid for other agents such as lidocaine, prilocaine, and cocaine, since the acute toxicity following intratracheal administration of these agents is less than that observed after intravenous injection. Fatal reactions have been reported following the intratracheal administration of tetracaine for topical anesthesia, which probably reflects the rapid absorption of this particular drug from this site of administration.[260]

Dosage

The absorption and subsequent blood level of local anesthetic agents are related to the total dose of drug administered regardless of the site of administration (Fig. 5-5). For most agents, there is a linear relationship between the amount of drug administered and the resultant peak anesthetic blood level. For example, the mean venous blood level of lidocaine increased from approximately 1.5 μg/ml to 4 μg/ml as the total dose administered into the lumbar epidural space was increased from 200 to 600 mg. For certain local anesthetic agents, e.g., etidocaine, a nonlinear relationship exists between the total dose administered and the peak venous blood level (Fig. 5-6). This nonlinear-

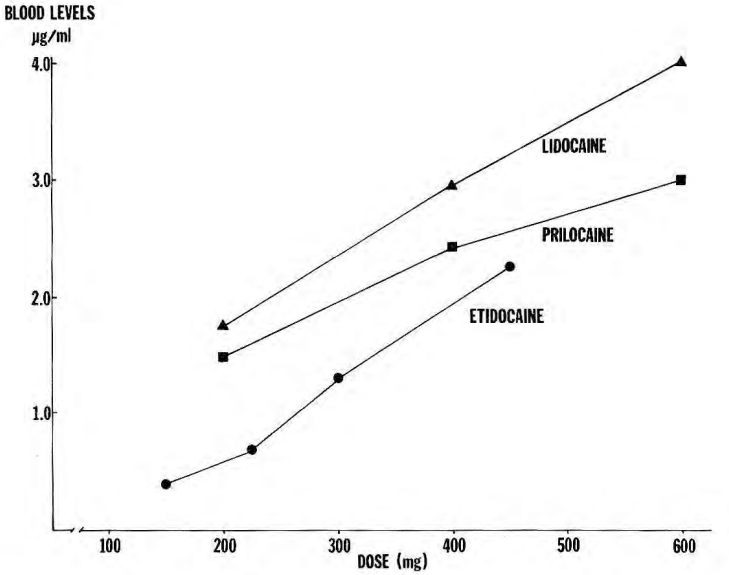


Fig. 5-5. Peak venous plasma levels following epidural administration of varying doses of different anesthetic agents.

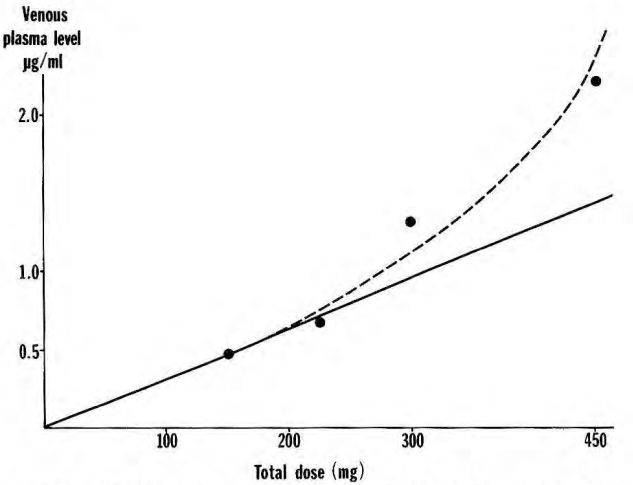


Fig. 5-6. Peak venous plasma levels of etidocaine following epidural administration. Dashed line represents actual drug levels; solid line represents predicted drug levels.

ity has been observed following the lumbar epidural administration of etidocaine and may reflect the high lipid solubility of this agent, which results in a sequestration of the drug such that the rate of systemic absorption is less when relatively small dosages are used. However, when large doses are administered, lipid-binding sites may be saturated so that free drug is available for systemic absorption.[140, 200]

The peak anesthetic blood level achieved following regional anesthesia is a function of the total dose of drug administered and does not appear to be related to either the concentration or volume of the local anesthetic solution employed (Fig. 5-7). No significant differences in lidocaine, prilocaine, and etidocaine blood levels have been observed following the intercostal and epidural administration of these agents at varying volumes and concentrations, if the total dose was constant.[143,200] Moreover, lidocaine was administered intramuscularly in concentrations varying from 2% to 10% and no significant difference in peak venous blood levels was observed when the total dosage administered was unchanged[254, 255] (Fig. 5-8). These results are consistent with the observations in Chapter 4 that anesthetic activity, in general, is related to the total dose of drug administered rather than to changes in concentration or volume of solution employed.

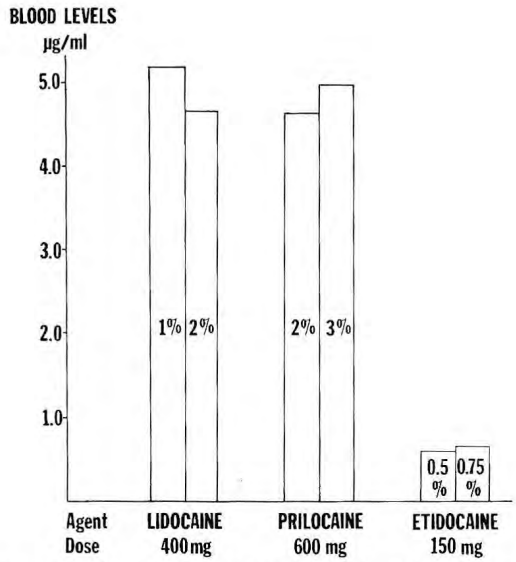


Fig. 5-7. Peak venous plasma levels following epidural administration of varying volumes and concentrations of several local anesthetic agents.

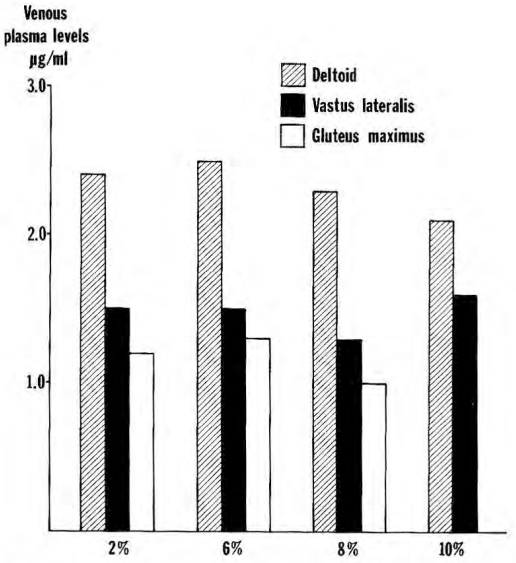


Fig. 5-8. Peak venous levels of lidocaine following intramuscular administration of varying concentrations and volumes of lidocaine (total dose = 300 mg).

Addition of Vasoconstrictor Agents

Many commercially prepared local anesthetic solutions contain a vasoconstrictor agent, usually epinephrine, in concentrations varying from 5 to 20 μg/ml. In addition, it is a common clinical practice to add epinephrine to plain solutions of local anesthetic drugs prior to their use for a variety of regional anesthetic procedures. The rationale for combining a vasoconstrictor agent with local anesthetic drugs is (a) to prolong the duration of action of certain local anesthetic agents by increasing neuronal uptake and (b) to decrease the rate of absorption from various sites of administration in order to reduce the potential systemic toxicity. Epinephrine in a concentration of 5 μg/ml (1:200,000) significantly reduces the peak blood levels of agents such as lidocaine and mepivacaine irrespective of the site of administration[143, 189] (Fig. 5-9). On the other hand, the peak blood levels of agents such as prilocaine, bupivacaine, and etidocaine appear to be minimally influenced by the addition of a vasoconstrictor substance[143, 200] (Fig. 5-9). The reasons for the apparent lack of absorption-retarding effect of epinephrine with these latter agents may differ depending on the specific drug. The lack of any difference between the peak blood levels of

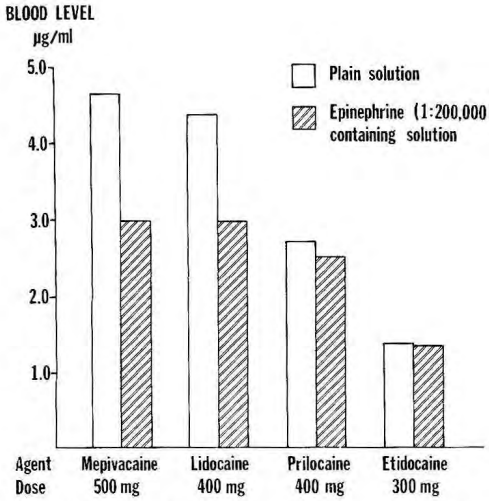


Fig. 5-9. Effect of epinephrine on peak blood levels of various local anesthetic agents administered epidurally.

prilocaine following the lumbar epidural administration of either plain prilocaine or prilocaine with epinephrine may be attributable mainly to the extremely rapid rate of tissue redistribution of prilocaine.[261, 262] In the case of bupivacaine and etidocaine, the apparent lack of influence of epinephrine following lumbar epidural administration may be related, in part, to the high lipid solubility of these two agents, which results in a significant uptake by epidural adipose tissue and, also, to the greater vasodilating potential of bupivacaine and etidocaine, which may counteract the vasoconstricting effect of epinephrine.[22, 263]

The concentration of epinephrine that appears to be optimal in terms of reducing the rate of absorption of a local anesthetic agent such as lidocaine and mepivacaine from the lumbar epidural space is 5 μg/ml (1:200,000). The use of a 1:80,000 concentration of epinephrine was not associated with a significantly greater reduction in the peak blood level of lidocaine.[212] Other vasoconstrictor agents, such as phenylephrine and norepinephrine, have been employed in combination with local anesthetic agents. However, neither phenylephrine nor norepinephrine in concentrations of 1:20,000 appears to be as effective in reducing the rate of absorption of lidocaine and mepivacaine as epinephrine 1:200,000.[214, 264]

Pharmacological Characteristics of Local Anesthetic Agents

If all factors such as site of administration, dosage, and vasoconstrictor are maintained constant, the rate of absorption of local anesthetic agents will be determined by the chemical and pharmacological properties of the specific drug (Table 32). A comparison of agents of equivalent anesthetic potency reveals that lidocaine and mepivacaine show similar peak venous blood levels following lumbar epidural administration. Prilocaine blood levels are significantly lower than either lidocaine or mepivacaine, which may reflect the greater vasodilator activity of these latter agents (Table 32). The rapid rate of elimination of prilocaine also contributes to its lower blood levels as compared to lidocaine and mepivacaine.[24] Similarly, a comparison of the two more potent local anesthetic agents, bupivacaine and etidocaine, reveals that the peak blood level of etidocaine is significantly lower than that of bupivacaine following the lumbar epidural administration of equal doses of these two agents.[200] These differences in peak blood levels may be related, in part, to variations in the lipid solubility of these agents (Table 32). In addition, the rate of tissue redistribution of etidocaine is more rapid than that of bupivacaine, which produces lower blood levels.[265]

Unfortunately, no studies are available to compare the blood levels of the ester-type agents, e.g., procaine, chloroprocaine, and tetracaine following various forms of regional anesthesia. This is due, in part, to the rapid hydrolysis of these agents by plasma cholinesterase, which makes it difficult to measure the blood level of these substances and so determine the relative rates of absorption. How-

Table 32

INFLUENCE OF VASODILATOR ACTIVITY AND LIPID SOLUBILITY ON LOCAL ANESTHETIC ABSORPTION FROM EPIDURAL SPACE

Agent	Relative Vasodilator Activity	Approximate* Lipid Solubility	Maximum Blood Levels (Epidural Administration)	
			Dose (mg)	Conc. (μg/ml)
LIDOCAINE	1	2.9	300	1.4
PRILOCAINE	0.5	1.0	300	0.9
MEPIVACAINE	0.8	0.8	300	1.5
BUPIVACAINE	2.5	27.5	150	1.0
ETIDOCAINE	2.5	141	150	0.5

*n-Heptane/pH 7.4 buffer

ever, blood flow studies have shown that procaine, chloroprocaine, and tetracaine cause vasodilation and, clinically, it is well known that epinephrine prolongs their anesthetic activity.[231,266] The only local anesthetic agent that consistently produces vasoconstriction is cocaine (Fig. 5-10). Direct blood flow measurements indicate that the initial effect of cocaine is one of vasodilation, followed by a prolonged state of vasoconstriction.[266] The mechanism of cocaine vasoconstriction is related to the inhibition of uptake of catecholamines into tissue-binding sites.[267] This inhibitory effect on catecholamine uptake, particularly norepinephrine, which results in less inactivation of circulatory norepinephrine, is ultimately responsible for the prolonged state of vasoconstriction observed after administration of cocaine.

DISTRIBUTION OF LOCAL ANESTHETIC AGENTS

The blood level of local anesthetic agents following absorption from the site of injection is a function of both (a) rate of distribution from the vascular compartment to tissue compartments and (b) elimination via metabolic and excretory pathways. Numerous reports are available in which the blood level of various local anesthetic agents has been measured. However, the values presented by different investigators may not be comparable due to variations in the defini-

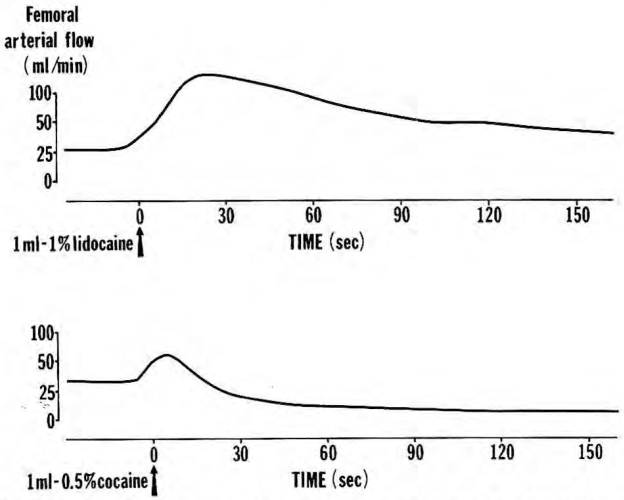


Fig. 5-10. Effect of intraarterial injection of lidocaine and cocaine on femoral arterial blood flow in the dog.

tion of the phrase "blood concentration".[268] The level of a local anesthetic drug in blood may be expressed in terms of the base or hydrochloride salt of the specific agent under study. Often no indication is given in publications concerning which form of the drug is measured. Blood levels of lidocaine expressed as the HCl salt are approximately 10% to 15% higher than corresponding values expressed as the lidocaine base. Concentrations of local anesthetic agents are usually determined in either whole blood or plasma. These data are not necessarily interchangeable, since the degree of plasma protein-binding of various agents determines whether they are equally distributed between plasma and red blood cells. For example, prilocaine is poorly protein-bound and is distributed fairly evenly between plasma and red blood cells such that plasma and whole blood concentrations of this agent are quite similar. On the other hand, agents such as bupivacaine and etidocaine, which are highly protein-bound, show marked differences between plasma and whole blood concentrations (Table 33). Whole blood concentrations are lower than the plasma levels of agents which are highly protein-bound. A final distinction concerning local anesthetic blood levels must be made between arterial and venous blood concentration measurements. Most studies involve the determination of anesthetic drug levels in venous blood because of the ease of sampling. However, arterial blood concentrations of local anesthetic agents have been determined and are significantly higher than venous blood levels during the initial 60 minutes following drug injection.[268]

The disposition kinetics of local anesthetic agents can be calculated best following intravenous administration. The shape of the curve relating anesthetic concentration in blood to time, following IV injection, is similar for all agents (Fig. 5-11). Two or three disap-

Table 33

RELATIONSHIP BETWEEN PLASMA PROTEIN BINDING OF VARIOUS LOCAL ANESTHETIC AGENTS AND THEIR CONCENTRATION IN WHOLE BLOOD, PLASMA AND ERYTHROCYTES

Agent	% Plasma Protein Binding	Whole Blood Conc / Plasma Conc	Plasma Conc / RBC Conc
PRILOCAINE	55	1.0	0.88
LIDOCAINE	64	0.8	1.34-2.1
MEPIVACAINE	77	0.7	2.6
ETIDOCAINE	94	0.5	7.5
BUPIVACAINE	95	0.5	7.8

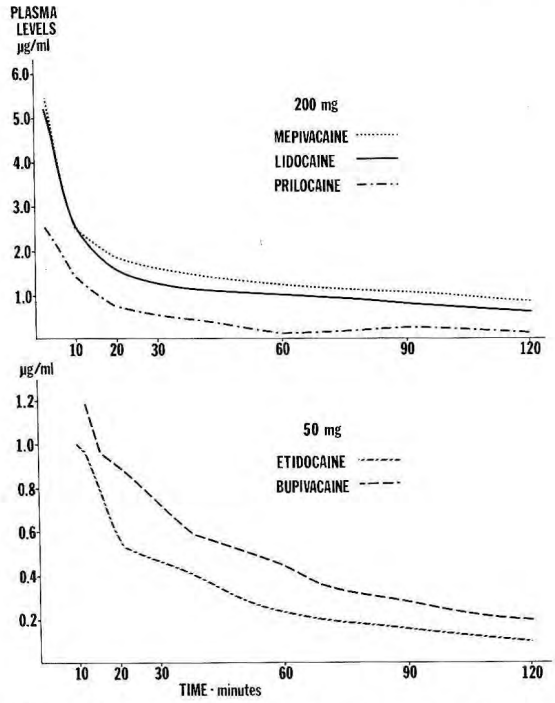


Fig. 5-11. Venous plasma levels of various local anesthetic agents following intravenous administration in man.

pearance phases have been described by various investigators.[259,265,268,269] The alpha phase represents the initial fast disappearance from blood into rapidly equilibrating tissues, i.e., tissue with a high vascular perfusion. A secondary slower phase of disappearance (beta phase) is a function of distribution to slowly equilibrating tissues and metabolism. This secondary disappearance phase has been subdivided by some workers into a beta phase, i.e., distribution to poorly perfused tissues and a gamma phase, i.e., elimination via metabolic and excretory paths.

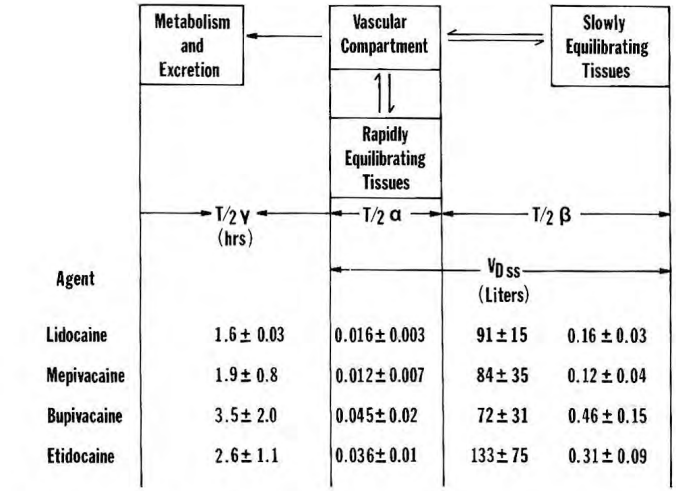
The rate of disappearance from blood usually is described in terms of the time required for a 50% reduction in blood concentration ($T½$ or $T/2$). It is common to utilize the symbols $T/2\ \alpha$, $T/2\ \beta$, $T/2\ \gamma$ for the various disappearance phases. Local anesthetic agents show different rates of disappearance from blood (Fig. 5-11). A comparison of the three amide drugs of similar potency and duration of action, i.e., lidocaine, mepivacaine, and prilocaine, reveals that the alpha and beta half-lives of prilocaine are significantly shorter than those of

mepivacaine and lidocaine, which indicates a more rapid rate of redistribution from blood to tissues (Fig. 5-11).[262] The rate of tissue redistribution for lidocaine and mepivacaine is quite similar. The more potent, longer-acting amide anesthetic agents, i.e., bupivacaine and etidocaine, possess higher $T/2\ \alpha$ and $T/2\ \beta$ values than the less potent agents of this class.[265,268] However, etidocaine possesses shorter alpha and beta half-lives than bupivacaine, which implies a more rapid rate of tissue redistribution (Fig. 5-11).[265,268] The rate of tissue redistribution appears related, in part, to the protein-binding and lipid solubility characteristics of the various agents. In general, compounds that are poorly protein-bound, e.g., prilocaine, and highly lipid soluble, e.g., etidocaine, distribute themselves more rapidly between blood and tissues.

The volume of distribution (V_D) is a calculated kinetic parameter which has been used to evaluate the distributive properties of drugs. V_D does not represent a true physiological space, but is indicative of the apparent distribution of a drug in the body with respect to the dose administered and the concentration in blood. The relative volume of distribution provides information concerning the differential uptake and accumulation of local anesthetic agents by various body tissues. For example, highly lipid-soluble drugs tend to accumulate in adipose tissue and so appear to have a large volume of distribution. Tucker and Mather have calculated the volume of distribution of various amide local anesthetic agents under steady state conditions, which they believe characterizes more accurately the relative distribution of the different drugs (Fig. 5-12).[268]

Local anesthetic agents are distributed throughout all body tissues, but the relative concentration in different tissues varies[24, 27, 270–272] (Fig. 5-13). In general, the more highly perfused organs such as the lung and kidney show higher local anesthetic concentrations than less well-perfused organs (Fig. 5-13). Skeletal muscle contains the highest percentage of the total injected dose of a local anesthetic agent, although the concentration of local anesthetic agent per gram of muscle tissue is not large. However, skeletal muscle is the largest mass of tissue in the body and serves as the greatest reservoir for local anesthetic agents.

Differences exist between the tissue levels of various local anesthetic agents. For example, Sung and Truant compared the distribution of procaine and lidocaine in rats and observed higher levels of lidocaine in fat tissue and in liver.[27] A comparative study of prilocaine and lidocaine in rats revealed the presence of significantly higher concentrations of prilocaine in lung tissue.[24] Mepivacaine



Agent	T/2 γ (hrs)	T/2 α	VD ss (Liters)	T/2 β
Lidocaine	1.6 ± 0.03	0.016 ± 0.003	91 ± 15	0.16 ± 0.03
Mepivacaine	1.9 ± 0.8	0.012 ± 0.007	84 ± 35	0.12 ± 0.04
Bupivacaine	3.5 ± 2.0	0.045 ± 0.02	72 ± 31	0.46 ± 0.15
Etidocaine	2.6 ± 1.1	0.036 ± 0.01	133 ± 75	0.31 ± 0.09

Fig. 5-12. Comparative pharmacokinetic properties of various local anesthetic agents calculated according to a three-compartment model.

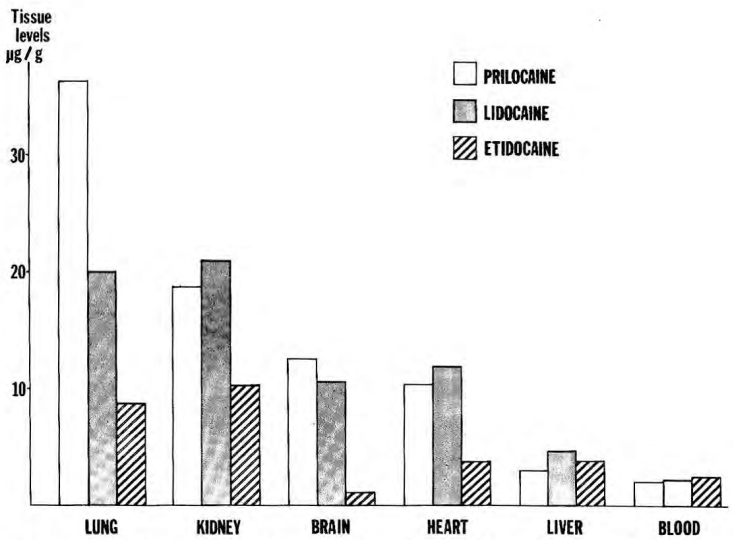


Fig. 5-13. Peak tissue levels of prilocaine, lidocaine, and etidocaine in guinea pigs following subcutaneous administration.

showed a distribution pattern similar to that of lidocaine, with a rapid accumulation in liver, kidney, salivary glands, and brain.[273] A comparison of the tissue levels of etidocaine and bupivacaine in guinea pigs demonstrated the previously mentioned accumulation of etidocaine in adipose tissue (Table 34).

Selective tissue distribution studies have been conducted in man. As indicated previously, the comparative plasma/erythrocyte (*P/E*) distribution of various local anesthetic agents has been determined and correlated directly with the relative protein-binding of the specific drugs (Table 33).[21,261] Prilocaine shows the lowest degree of plasma-protein-binding and the lowest *P/E* ratio, whereas bupivacaine is bound to the greatest degree to plasma proteins and has the highest *P/E* ratio.

The degree of uptake of local anesthetic agents by skeletal muscle also has been approximated in man by the simultaneous measurement of anesthetic blood levels in brachial artery and antecubital vein. The peripheral venous/arterial blood concentration ratio for lidocaine was reported to be 0.73 ± 0.003 compared to a value of 0.47 ± 0.003 for prilocaine, which is indicative of the more rapid tissue redistribution of prilocaine.[261] Similar studies with bupivacaine and etidocaine reveal 20% to 40% higher levels of these agents in arterial samples than in simultaneously drawn venous samples.[209, 268] These studies in man are consistent with the distribution studies in animals, which indicate a rapid tissue uptake for all local anesthetic agents, but differences in the rate and degree of tissue redistribution between specific local anesthetic drugs as a function of their intrinsic physicochemical properties.

The rate of tissue uptake of local anesthetic agents will be influenced by the physiological status of the subject.[273] The rate of

Table 34

TISSUE (μg/g)/BLOOD (μg/ml) RATIOS OF ETIDOCAINE AND BUPIVACAINE IN THE GUINEA PIG

TISSUE	ETIDOCAINE	BUPIVACAINE
BRAIN	1.3	3.5
HEART	1.8	3.9
FAT	7.8	4.4
MUSCLE	0.8	1.3

lidocaine disappearance from blood is significantly prolonged in patients with a decreased vascular perfusion of tissues secondary to impaired myocardial contractility.[274] The arteriovenous difference of lidocaine and etidocaine was considerably greater in human volunteers undergoing epidural blockade compared to surgical patients during the initial 60 minutes following administration into the lumbar epidural space. These data suggest a more rapid rate of tissue uptake by the healthy volunteers.[268]

A special category of local anesthetic distribution involves placental transmission and uptake by fetal tissue. Considerable information has been obtained in recent years concerning the placental transmission of local anesthetic agents.[275–286] In general, local anesthetic drugs appear to cross the placenta by passive diffusion. However, the rate and degree of diffusion vary considerably between specific agents and appear to be inversely correlated with the degree of plasma-protein-binding (Table 35).[287] Prilocaine shows the highest umbilical vein/maternal blood (*UV/M*) ratio (1.00–1.08) and lowest plasma-protein-binding capacity (55%).[279, 281] On the other hand, the *UV/M* ratio of bupivacaine and etidocaine is 0.14–0.44 and these agents are approximately 95% protein-bound.[282, 285, 286] Lidocaine and mepivacaine occupy an intermediate position both in terms of placental transmission (*UV/M* ratio of 0.52–0.71) and protein-binding (64–77%).[275–278,280,283,284]

The placental transmission of local anesthetic agents does not appear to be influenced by the route of administration. For example, the *UV/M* ratio of lidocaine was similar following paracervical, lumbar epidural, and IV administration.[277, 278] The peak venous plasma level of local anesthetic agents in maternal blood also does not affect placental transfer. The *UV/M* ratio of mepivacaine in two separate investigations were similar (0.69 and 0.71), whereas the maternal blood levels showed a twofold difference (2.9 and 6.9 μg/ml).[275, 280]

Table 35

RELATIONSHIP BETWEEN PLASMA PROTEIN BINDING CAPACITY AND UMBILICAL VEIN/MATERNAL BLOOD (UV/M) RATIO OF VARIOUS LOCAL ANESTHETIC AGENTS

Agent	Protein Binding Capacity %	Maternal Arterial or Venous Blood Levels (μg/ml)	Umbilical Vein Levels (μg/ml)	UV/M Ratio
PRILOCAINE	55	1.03-1.5	1.07-1.5	1.0-1.18
LIDOCAINE	64	1.23-3.5	0.8-1.8	0.52-0.69
MEPIVACAINE	77	2.91-6.9	1.9-4.9	0.69-0.71
BUPIVACAINE	95	0.26	0.08-0.11	0.31-0.44
ETIDOCAINE	94	0.25-1.3	0.07-0.45	0.14-0.35

The comparative maternal and fetal tissue distribution of local anesthetic drugs have been investigated by Finster and co-workers in guinea pigs.[288, 289] Although the distribution of lidocaine in maternal and fetal tissues was generally similar, certain differences did exist (Table 36). For example, significantly higher levels of lidocaine were found in fetal liver than in adult liver. This may be indicative of poorly developed enzyme systems in the fetus such that amide-type local anesthetic drugs may not be metabolized as rapidly in fetal liver as in adult liver. Studies comparing etidocaine and lidocaine revealed a greater uptake by fetal brain of etidocaine than of lidocaine.[289] Etidocaine tends to accumulate in peripheral fat in adults; the lack of peripheral fat depots in the fetus could result in the uptake of this agent by other lipid organs such as brain. In summary, the placental transmission of local anesthetic agents is influenced mainly by the degree of maternal plasma-protein-binding of the various agents and the rate of fetal tissue uptake.[290] Fetal plasma-binding of local anesthetic agents is approximately 50% less than binding in maternal plasma, so that more unbound drug is present in the fetus.[291] Those drugs that demonstrate the highest degree of protein-binding also tend to be more lipid soluble, such that the rate of tissue uptake of the unbound drug is enhanced. Thus, the maternal/fetal anesthetic blood concentrations may differ markedly between agents, but the total amount of drug transferred across the placenta may be similar for agents of high and lower protein-binding capacity. The clinical significance of these findings is not certain. It was originally postulated that agents which possess a high protein-binding capacity should be potentially less toxic for the fetus.[22] However, if the rate of fetal tissue uptake is greater for drugs of high protein-binding and high lipid solubility, then the potential fetal toxicity would be similar for all of the local anesthetic compounds.

Table 36

COMPARATIVE GUINEA PIG MATERNAL AND FETAL TISSUE LEVELS OF LIDOCAINE

TISSUE	PEAK MATERNAL LEVEL	PEAK FETAL LEVEL
BLOOD (μg/ml)	7.6	3.6
MYOCARDIUM (μg/g)	17.2	8.9
BRAIN	31.9	9.7
KIDNEY	42.3	5.8
LIVER	7.8	22.9

METABOLISM

The metabolism of local anesthetic agents is related to their basic chemical structure. As indicated previously, the clinically useful compounds can be separated into two general classes: agents containing an ester linkage (e.g., procaine and tetracaine) and agents containing an amide linkage (e.g., lidocaine and mepivacaine).

Ester Compounds

The ester or procaine class of local anesthetic drugs are hydrolyzed in plasma by the enzyme, pseudocholinesterase.[26] The rate of hydrolysis may vary markedly between agents in this chemical class.[23] Chloroprocaine shows the most rapid rate of hydrolysis (4.7 μmoles/ml/hour), while a rate of 1.1 μmoles/ml/hour was observed for procaine and 0.3 μmoles/ml hour for tetracaine[23] (Table 3). The anesthetic quality and potential toxicity of ester-type agents appear to bear an inverse correlation to the rate of hydrolysis. Thus, tetracaine, which exerts the longest duration of anesthesia and is the most toxic of the ester-type local anesthetic agents, undergoes the slowest rate of hydrolysis, whereas 2-chloroprocaine, which possesses the shortest duration of anesthetic action and is the least toxic agent, is the most rapidly hydrolyzed. Procaine occupies an intermediate position, both in terms of anesthetic duration, systemic toxicity, and rate of hydrolysis. This type of metabolic pathway has specific clinical relevance, since subjects with atypical forms of pseudocholinesterase may be incapable of hydrolyzing agents of the procaine-type, which could result in a prolongation of systemic toxic effects.[292]

Some of the metabolites formed by the hydrolysis of the various ester-type agents have been identified.[26] For example, procaine undergoes cleavage at the ester linkage to form para-aminobenzoic acid and diethylamino ethanol. Para-aminobenzoic acid then is excreted unchanged in the urine, whereas diethylamino ethanol may undergo further metabolism. The type of metabolites formed from the parent local anesthetic compounds also is of clinical significance. The allergic phenomena which occur more frequently with the use of the ester-type local anesthetic agents are not related to the parent compounds, such as procaine and tetracaine, but are attributable to the formation of para-aminobenzoic acid, the primary metabolite formed from the hydrolysis of procaine, chloroprocaine, and tetracaine.

Amide Compounds

The metabolism of the amide-type anesthetic agents is more complex than that of the ester agents. A number of studies performed in animals and man have revealed that the liver is the prime site of metabolism for these amide-type drugs. Sung and Truant compared the rate of metabolism of lidocaine incubated with various rat tissue slices and found the liver to be the most active organ for metabolizing this agent.[27] Similar in vitro studies with mepivacaine have shown that this agent is readily metabolized by rat liver slices incubated under aerobic conditions.[28] Prilocaine appears to differ somewhat from lidocaine and mepivacaine. Although this agent is readily metabolized by rat liver slices, some degradation also occurs when prilocaine is incubated with kidney slices.[293] Isolated liver perfusion studies with bupivacaine and etidocaine have revealed that these compounds also undergo hepatic degradation.[294]

In vivo studies have confirmed the in vitro tissue slice data, indicating that the liver is the prime site of metabolism for local anesthetic agents of the amide-type. Studies in rats have shown that hepatectomy results in substantially higher tissue levels of lidocaine and an increase in the anesthetic activity and duration of toxic symptoms produced by this agent.[27] The rate of disappearance of lidocaine from blood was also found to decrease in hepatectomized dogs and in patients whose livers had been removed during the course of liver transplantation.[295]

Differences exist between the amide-type local anesthetic agents with regard to their relative rates of metabolism (Table 37).[24, 28, 294] Prilocaine has been shown to undergo the most rapid rate of degradation in liver slices, whereas the rate of metabolism of lidocaine, mepivacaine, bupivacaine, and etidocaine appear to be similar. The degradation of the amide-type local anesthetic agents is influenced by the hepatic status of the individual subject. Simultaneous measurements of arterial and hepatic venous levels of lidocaine and estimations of hepatic blood flow have shown that approximately 70% of injected lidocaine is metabolized in subjects with normal liver function.[296] In patients in whom liver blood flow is abnormally low, or in whom liver function is poor or nonexistent, the breakdown of the amide-type of local anesthetic agent is markedly decreased, resulting in significantly higher blood levels which, in turn, may potentially lead to greater toxicity of this class of drugs.[295] Indeed, systemic reactions to lidocaine have been reported in patients with severe hepatic disease.[297]

Table 37

COMPARATIVE RATES OF METABOLISM AND METABOLITES OF VARIOUS AMIDE LOCAL ANESTHETIC AGENTS

Agent	Metabolic rate*	Chemical nomenclature	Metabolic products
PRILOCAINE	>90	2-propylamino-o-propionotoluidide	o-toluidine, L-N-n-propylamine
LIDOCAINE	62	Diethylaminoacet-2,6-xylidide	monoethylglycinexylidide, 3-hydroxy-lidocaine, 3-hydroxy-monoethylglycinexylidide, 2,6 xylidine, glycinexylidide, 4-hydroxy-2,6-dimethylaniline, 2-amino-3-methylbenzoic acid
MEPIVACAINE	55	1-N-methylpipecolic acid 2,6-dimethylanalide	2,6-pipecoloxylidide-3-hydroxy-1-methyl, 2,6-pipecoloxylidine, 2,6-pipecoloxylidide 4-hydroxy-1-methyl
BUPIVACAINE	54	1-butyl-2,6-pipecoloxylidide	2,6-pipecoloxylidine
ETIDOCAINE	67	2-(N-ethylpropylamino)-2,6-butyroxylidide	2,6 xylidine, 2-ethylamino-2,6-butyroxylidide, 2-propylamino-2,6-butyroxylidide, 2-amino-butyroxylidide

*Percent metabolites appearing following 10-30 minutes of incubation or perfusion of guinea pig or rat liver slices

Although many of the primary metabolites of the various amide agents have been identified (Table 36),[298] the complete spectrum of metabolic products derived from the compounds in this class has not been elucidated. The metabolism of lidocaine has been studied most extensively (Fig. 5-14). Hollunger originally proposed a metabolic pathway for the degradation of lidocaine in rat and rabbit liver.[299] The initial step involved the oxidative deethylation of lidocaine to monoethylglycinexylidide and acetaldehyde. Monoethylglycinexylidide subsequently was hydrolyzed to xylidine and monoethylglycine. Xylidine itself underwent further oxidation to some unknown product. Keenaghan and Boyes summarized the information available concerning the metabolism of lidocaine in various animals species and demonstrated considerable species variability.[300] Significant amounts of monoethylglycinexylidide and xylidine were recovered from guinea pig urine. Rats formed large quantities of the meta-hydroxy derivative of both lidocaine and monoethylglycinexylidide. These phenolic derivatives appear to a limited extent in dogs and man. The conjugates of these two metabolites were extensively recycled in the bile of rats. However, these metabolites were essentially lacking in man, which suggests that biliary recycling is not a significant pathway for lidocaine elimination in man. Hydroxyxylidine was the major metabolic product of lidocaine found in dog and human urine. The dog and human were most similar in terms of lidocaine metabolism, whereas the rat and man appeared quite dissimilar. A number of

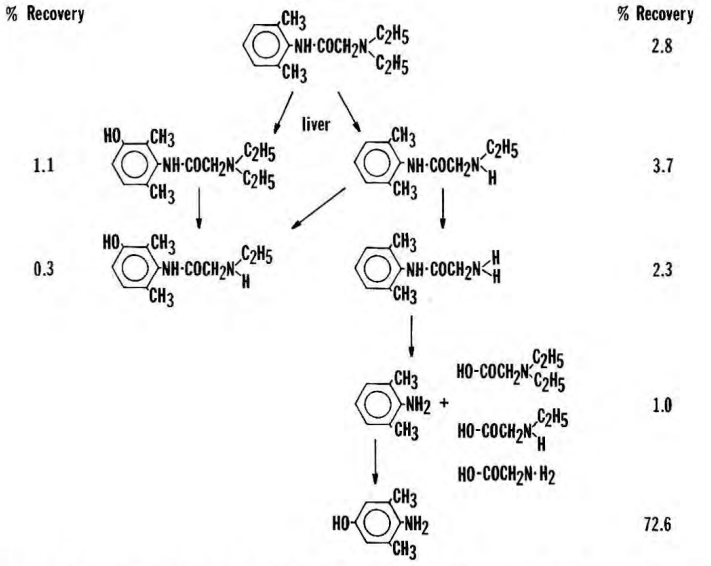


Fig. 5-14. Suggested metabolism of lidocaine in man and percent recovery of various metabolites in human urine.

minor metabolites of lidocaine have been described by various investigators.[301, 302] However, some confusion has existed concerning whether these substances are actually formed from the degradation of lidocaine or represent artifacts of the experimental analytical system.[303, 304]

The metabolism of mepivacaine has been studied in liver slice preparations from mice and rats, and n-demethylation appears to be the initial step in the degradation of this agent in these species.[28] Hydroxylation of mepivacaine also occurs in rats and man, and as observed with lidocaine, approximately 60% of the dose of mepivacaine administered to rats is excreted as an aromatic hydroxy derivative.[305]

In man, conjugates of these hydroxy metabolites of mepivacaine account for 25% to 40% of the administered dose of mepivacaine.[305, 306] In addition, three neutral metabolites of mepivacaine have been identified in human urine,[307] but approximately 50% of administered mepivacaine remains unidentified. Meffin, Long, and Thomas have also studied the metabolism of mepivacaine in human neonates and suggest that the newborn is not capable of aromatic hydroxylation of mepivacaine.[308]

The metabolism of prilocaine differs significantly from that of

lidocaine and mepivacaine, due apparently to the lack of one methyl group on the aromatic portion of the molecule (Table 1). o-toluidine and L-N-n-propylamine have been identified as metabolites of prilocaine.[293] These substances also may undergo further degradation.

Detailed metabolic data are not available on the newer amide-type of local anesthetic agents, i.e., bupivacaine and etidocaine. Preliminary studies by Reynolds in which the metabolism of bupivacaine and mepivacaine was compared in human volunteers revealed that approximately 5% of the dose of bupivacaine administered was recovered in urine as the N-dealkylated metabolite, pipecolylxylidine.[309] Goehl and associates studied the metabolism of bupivacaine in rats and monkeys and observed that the rat excretes substantial quantities of bupivacaine as an aromatic hydroxy metabolite, whereas the monkey excretes over 50% of the dose as the hydrolysis product, pipecolic acid.[310]

Preliminary data on the metabolism of etidocaine, which is structurally similar to lidocaine, have shown that only 1.1% of the administered dose of etidocaine was recovered in guinea pig urine as the secondary amine metabolite, whereas 14.9% of lidocaine was identified as the secondary amine metabolite.[298] The excretion of 2,6-xylidine in guinea pigs was also considerably lower following etidocaine administration (2.2%) than following lidocaine administration (16.2%). The presence of the branched alkyl chain in etidocaine probably results in metabolic products that are markedly different than those of lidocaine.

The products formed from the degradation of the amide-type local anesthetic agents may have clinically significant implications. Under normal physiological conditions, these metabolites exert relatively insignificant pharmacological or toxicological effects. In certain situations, however, such as renal or cardiac failure, or during prolonged periods of administration, these metabolites might accumulate and exert significant clinical effects. For example, certain metabolites of lidocaine have been shown to possess antiarrhythmic and toxicological properties similar to, but less potent than, that of the parent compound lidocaine.[311] Other lidocaine metabolites may accumulate in the plasma of patients following prolonged intravenous therapy with lidocaine for control of cardiac arrhythmias and may produce systemic toxic effects that are additive to the inherent toxicity of the parent compound, lidocaine.[312] The prime example of a metabolite being responsible for the toxicity of a local anesthetic agent is the methemoglobinemia that occurs in patients treated with

large doses of prilocaine.[25] Prilocaine, itself, is not capable of producing methemoglobin. However, o-toluidine, which is one of the main metabolites of prilocaine, can induce the formation of methemoglobin in vitro and is believed responsible for the methemoglobinemia observed in man.

EXCRETION

The kidney is the main excretory organ for local anesthetic agents and their metabolites. Among the ester class of local anesthetic drugs, procaine is hydrolyzed almost completely in plasma and less than 2% of unchanged drug is excreted by the kidney.[26] Approximately 90% of para-aminobenzoic acid, the primary metabolite of procaine, is found unchanged in the urine, whereas only one-third of diethylaminoethanol, the other metabolite, is excreted unchanged. Similarly, only small amounts of unchanged chloroprocaine and tetracaine are found in urine.

Only small amounts of the amide-type local anesthetic agents are excreted unchanged via the kidneys. Less than 10% of intravenously administered lidocaine was found in the urine of human volunteers.[300, 313] Approximately 80% of administered lidocaine could be recovered in human urine in the form of various metabolites.[300] From 1% to 16% of administered mepivacaine appears as unchanged drug in human urine, whereas 25% to 40% is excreted as degradation products.[305,306,309] Only 16% of unchanged bupivacaine has been recovered from human urine.[309] Cocaine is the only local anesthetic agent of either the ester or amide-type that is excreted mainly in an unchanged form in kidney.[245]

A study of the comparative renal clearance of prilocaine and lidocaine in man by Eriksson and Granberg indicated a substantially higher clearance value for prilocaine, which they believed to be related to the lower protein binding of prilocaine.[314] The renal clearance of both prilocaine and lidocaine was found to be inversely proportional to the pH of urine, which suggests that the urinary excretion of these agents occurred by nonionic diffusion. This finding may have practical clinical implications, since urinary acidification may provide a means of increasing the excretion of local anesthetic agents in patients in whom toxic symptoms develop.

Biliary excretion appears to play a role in the disposition of local anesthetic agents in certain animal species. Lidocaine, mepivacaine, and tetracaine or their metabolites have been isolated from

bile.[1, 28, 300, 315] In rodents, unchanged tetracaine is excreted by way of the common bile duct into the gastrointestinal tract and then completely reabsorbed into blood, where hydrolysis occurs. The metabolites are ultimately excreted via the kidneys. On the other hand, lidocaine and mepivacaine undergo hepatic degradation initially, following which some of the metabolites are excreted by way of the common bile duct into the gastrointestinal tract. The metabolites are then completely reabsorbed and ultimately appear in urine. The biliary excretion and recycling of lidocaine appear to be important in eliminating this agent in rats, but probably are not significant in either dog or man.[298]

SUMMARY

1. The physiological disposition of local anesthetic agents can be summarized as follows (Fig. 5-15): (1) complete absorption from the site of injection into the central vascular compartment; (2) redistribution throughout total body water according to a 2- or 3-compartment pharmacokinetic model, with the rate of tissue redistribution varying as a function of such physicochemical properties as protein-binding capacity and lipid solubility; (3) metabolism of the ester-type agents in blood by the enzyme, pseudocholinesterase, with amide agents undergoing degradation primarily in the liver; (4) biliary recycling of the parent compound itself or metabolites in some animal species; (5) excretion of the remaining unchanged drug and metabolites via the kidney into the urine.

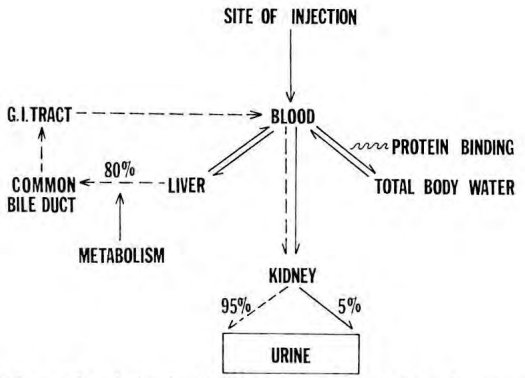


Fig. 5-15. Physiological disposition of local anesthetic agents.

2. The metabolism and elimination of local anesthetic agents can be significantly influenced by the clinical status of the patient which, in turn, may effect the potential toxicity of this class of compounds. For example, the average half-life of lidocaine in blood of approximately 90 minutes in normal subjects is markedly prolonged in patients with significant degree of cardiac failure. The rate of hydrolysis of the ester agents is decreased in patients with atypical forms of the enzyme, pseudocholinesterase, while hepatic dysfunction will result in an accumulation of the amide-type local anesthetic agents. The kidney is the prime excretory organ for both unchanged drug and the metabolites of local anesthetic agents. A significant impairment of renal function may result in increased blood levels of the parent compound or its metabolites which may cause adverse systemic effects.