THE RELATIONSHIP BETWEEN PHARMACOKINETICS AND TOXICITY OF LOCAL ANAESTHETICS – IMPLICATIONS FOR DOSE SELECTION

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INTRODUCTION

Local anaesthetic agents are relatively safe when administered in the proper dosage at appropriate anatomical sites. In clinical practice, local anaesthetic intoxication principally occurs after accidental iv bolus injection or when a sizeable dose is rapidly absorbed systemically. The systemic toxicity of local anaesthetics mainly involves the central nervous system (CNS) and the cardiovascular system (CVS).[1] These toxic reactions are straightforward, time-and dose-dependent phenomena.

Plasma concentration profiles and the potential for systemic toxicity following perineural administration of a local anaesthetic depend on the administered dose and the balance between the rate processes involved in drug absorption and systemic disposition. Pharmacokinetics provides a mathematical basis for the description and prediction of the time course of drugs in the body, including events after inadvertent intravascular injection. It also helps to identify patients who may be at particular risk of developing systemic toxic reactions.

PHARMACOKINETICS: SYSTEMIC AND REGIONAL

The systemic pharmacokinetics of local anaesthetics during regional anaesthesia consist of systemic absorption and systemic disposition, the latter consisting of distribution and elimination. Circulating blood concentrations are used to determine both processes. Concentration peaks occur earlier in arterial blood than in vital organs, and there is an arterio-venous difference. Concentrations in peripheral blood may peak later than those in the brain. It is not possible to study the pharmacokinetics of drugs in human brain or heart, where toxicity occurs. Regional pharmacokinetics is based on the study of the factors influencing drug concentrations in specific regions (tissues, organs) of the body due to the movement of drug from blood in and out of the region (drug 'uptake' and 'elution', respectively).[2] In this way it is possible to correlate drug effect with tissue concentrations, and to observe any relationship between organ drug concentration and symptoms in that organ.[3,4] Regional pharmacokinetics are based on the principle of mass balance. Mass balance parameters give a measure of the net rate of exchange between blood and tissue. The cumulative time integral of the net flux gives the corresponding tissue concentrations.
**Systemic Pharmacokinetics after Inadvertent I.V. Injection**

After inadvertent iv injection, lung and protein binding affect the likelihood of toxicity.

**The Role of the Lungs**

After inadvertent iv injection, local anaesthetics pass through the lung before entering the arterial circulation. The lung absorbs a sizeable fraction of local anaesthetic during the first circulations, principally in the first minute. They thereby modulate the arterial concentration [5], and less drug reaches the brain and the heart. However, drug is released from the lung quite rapidly after the initial uptake. The capacity of the lung to bind basic drugs is probably saturable. However, it can be assumed that following inadvertent iv injection of a clinical dose of local anaesthetic intended for extradural injection, the lung will attenuate drug blood concentrations to some extent.

**The Role of Plasma Protein Binding**

Toxic effects are probably more closely related to free than to total (bound plus free) plasma or blood concentrations, thus protein binding is important when relating plasma concentrations to systemic toxicity.[2,6,7] Theoretically, plasma binding could limit the first-pass uptake of local anaesthetics into the brain and myocardium following rapid inadvertent i.v. injection, thereby modulating toxicity. In fact, it has only a minor effect on the rate and extent of initial distribution of local anaesthetics in the brain and in the heart.[8,9] Rapid intracarotid injection of bupivacaine and lignocaine in rats shows that the fraction of intra-vascular drug available for brain extraction is generally larger than the initial free fraction of drug entering the capillary bed.[8,9] Thus uptake into the brain, and presumably heart, is not limited to the free drug.

**Regional Pharmacokinetics after Inadvertent (I.V.) Injection**

The brain and the heart are the main target organs for systemic toxicity.

**Uptake into the Brain**

Studies in sheep have shown that increasing the rate of drug administration decreases the convulsant dose.[10,11] Factors that may modify the CNS threshold concentration of a local anaesthetic include its chemical structure and its rate of administration, as well as the temperature and acid-base balance of the patient.[1] Concentrations in brain tissue are much greater than corresponding arterial blood concentrations.[11] Tissue uptake may be affected by changes in plasma or tissue pH.

**Uptake into the Heart**

Local anaesthetic cardiovascular toxicity results from its effects on smooth and cardiac muscle. Direct and indirect effects may play a role, as local anaesthetics affect the mechanical and electrical activities in the heart. Myocardial depressant effects of local anaesthetics after inadvertent i.v. injection may become reversed with the onset of overt CNS excitation, but electrocardiological effects may be exacerbated. Left coronary artery infusions of local anaesthetics in a conscious sheep model precludes CNS actions.[12] So there will be no recirculation of the drug to cause CNS effects. Blood and tissue drug concentration were similar for bupivacaine, levobupivacaine and ropivacaine. In isolated rabbit hearts, bupivacaine and lignocaine exhibit an almost similar myocardial uptake and disposition profile.[13] Differences in cardiac effects between the above drugs are probably more related to differences in direct cardiac depression than to differences in myocardial uptake and disposition kinetics.[14]

**Systemic Pharmacokinetics after Accurate Perineural Injection**

When systemic input of local anaesthetic is gradual as with a successful perineural injection, absorption, distribution and elimination may play a role.

**Systemic Absorption**

For any local anaesthetic, the rate of vascular absorption decreases (in descending order) for intercostal, caudal, epidural, brachial plexus, sciatic/femoral. The recommended maximum dose of local anaesthetic thus varies.
THE ROLE OF THE LUNGS

With slow drug input after a correctly administered regional block, the difference between systemic arterial and pulmonary arterial concentrations profiles is minimal. Sharrock and colleagues demonstrated that, 10% of the local anaesthetic was absorbed during the first 5 minutes after accurate epidural administration of both enantiomers of bupivacaine.[15]

ROLE OF PROTEIN BINDING

Gradual input should cause little effect on free (active) drug concentrations since any change in protein binding is likely to be buffered by the more extensive tissue binding, and with some local anaesthetics, a change in clearance. Long-term epidural infusion of bupivacaine for the relief of postoperative pain however results in progressively increasing plasma concentrations.[16,17] Opposing changes in the protein binding of bupivacaine are likely to occur postoperatively, because plasma ?1-acid-glycoprotein (AAG) increases progressively during the first postoperative days.[18] Under such conditions of pseudoequilibrium, CNS toxicity correlates better with unbound (active) drug concentrations than with total drug (bound plus free drug) in the plasma. This is also demonstrable in animals, in which lignocaine brain/serum partitioning is limited by its binding to AAG.[19]

EFFECTS OF PATIENT VARIABLES AND OTHER DRUGS ON THE PHARMACOKINETICS

Some patients may absorb local anaesthetics more rapidly and dispose of them more slowly, and thus be at greater risk of toxicity after normal dosage. Ageing, congestive heart failure, renal and hepatic disease may alter the elimination of the amino-amides.[20-24] This may lead to increased accumulation, increasing the risk of systemic side-effects, including toxicity. In pregnant women bupivacaine concentrations accumulate slowly during continuous epidural administration.[25]

Propanolol and cimetidine reduce the clearance of local anaesthetics, mainly by inhibition of mixed function oxidase activity, with a smaller contribution from decreased liver blood flow.[26,27]

CONCLUSION

Human studies do not allow a great deal of insight into toxicity, but animal studies have allowed the various factors to be separated. Important pharmacokinetic factors in local anaesthetic toxicity include the drug, route of injection, speed of injection, lung uptake, pH, coronary and coronary blood flows. A knowledge of plasma binding is essential for the correct interpretation of “blood level” data, but is of minor significance in controlling access of the drugs to the sites of toxicity. [28]
REFERENCES

14. Ladd LA, Chang DH-T, Wilson K, Copeland S, Plummer JL, Mather LE. Effects of CNS site-directed carotid arterial infusion of local anesthetics in sheep. Anesthesiology (accepted for publication)