Chapter 8

Drug interactions and systemic toxicity

H. Adriaensen

The title of this contribution covers a large field of the pharmacological literature, and it is not easy to treat all aspects of the subject. Therefore we have defined the scope.

1. The starting point for the discussion will be the pharmacology of local anaesthetics (LA). The oral, parenteral or locoregional use of opioids, non-steroidal anti-inflammatory drugs, NMDA-antagonists, a2 agonists or any other analgesic substances in the absence of LA will not be the subject of this paper.

2. Established techniques such as the combined use of LA with opioids will only be treated as far as new insights or innovative applications are concerned.

Hence, it is not our intention to conduct a meta-analysis or present a comprehensive review. We have chosen to search for data in the recent literature (Medline 1995-1998) and to focus on publications that triggered our interest.

Although we were very impressed by the editorial “The systematic review: a good guide rather than a guarantee” [1], we fear that our review will not meet the criteria specified in that editorial: it will not be based on a complete review of the published material; it will not only refer to randomized controlled trials; and it will in some way reflect a personal viewpoint.

To justify such an approach we forward the following arguments:

– the title of this manuscript covers not one, but two subjects: drug interactions and systemic toxicity;

– we already restricted the field to LA but there are several LA agents and many routes of administration, each leading to different drug interaction patterns and systemic toxicity problems;

– when searching the Medline with the key words “drug interactions”, “systemic toxicity” or “adverse events” in combination with “local anaesthetics” (or local anaesthetics), or with one of the specific agents i.e. “lidocaine”, “bupivacaine”, “prilocaine”, hundreds of abstracts are generated.

The poorly delineated subject, the heterogeneity of the drugs and the large amount of retrieved material are the reasons why we opted for a more eclectic discussion of the subject and for reporting mainly on papers thought to be clinically relevant or innovative: our aim is to update background knowledge and to furnish some additional information to the interested reader.

We have divided the paper into two parts:
Drug interactions

Drug-Drug Interaction is one factor among many others that may affect the therapeutic outcome of drug administration [2].

A potential drug interaction refers to the possibility that one drug may alter the intensity of the pharmacological effect of another drug given concurrently. The net result may be enhanced or diminished effects of one or both drugs, or the appearance of a new effect that is not seen with either drug alone.

Interactions may be either pharmacokinetic (i.e., alterations of absorption, distribution, biotransformation or excretion of one drug by another) or pharmacodynamic (i.e., drugs that interact at a common receptor site or that have additive or inhibitory effects due to actions at different sites in an organ). An additive, synergistic, potentiating or antagonizing action may be the final result [3].

Pharmacokinetic interactions

Several pharmacokinetic interactions of LA with commonly used drugs have been documented. One of the drugs most commonly used in connection with LA is 1/200 000 adrenalin added to the LA solution in order to increase the intensity of neural blockade, to prolong the action of the LA, and to decrease its absorption. Mazoit et al. [4] were able to show that, when epidurally administered, clonidine can also alter the pharmacokinetics of lidocaine: like adrenaline it may decrease lidocaine plasma peak concentrations ($C_{\text{max}}$), thus leading to a decreased toxicity.

Protein binding can also be affected. The use of oral contraceptives decreases the $\alpha$-acid glycoprotein, the fraction of plasma proteins that binds LA of the amide group [5]. Particularly bupivacaine and ropivacaine have a high protein-bound fraction.

A competitive binding of diazepam vs bupivacaine to plasma proteins with a larger free fraction of bupivacaine available for metabolism and elimination could explain the shorter half-life of bupivacaine under conditions of co-administration [6].

Drugs that decrease hepatic blood flow or enzymatic activity can decrease the clearance of the amide-type LA. Such an interaction has been described for propanolol [7] and cimetidine [8], when used in combination with lidocaine.

LA of the ester type agents (procaine-chloroprocaine and tetracaine) under-