DRUG INTERACTIONS AND INTRAVENTRICULAR CONDUCTION DISORDERS INDUCED BY BUPIVACAINE

Q. Timour, Ph.D., M. Freysz, M.D., L. Bertrix, M.D., Ph.D., P. Couzon, M.D., J. Lang, M.D., Ph. D., G. Faucon, M.D., Ph. D.

Department of Medical Pharmacology, Cl. Bernard University, 69008 Lyon (France).

Introduction. The depressant properties manifested by bupivacaine (Bup) on intraventricular conduction are insufficient to account for incidents such as His bundle branch blocks, 2nd or 3rd degree atrioventricular blocks, and reentrant arrhythmias, unless plasma concentrations exceed 6.0 - 8.0 µg/ml. Such levels are usually associated with inadvertent i.v. injection of the drug, when transiently concentrations may exceed 25.0 µg/ml (1). In the course of an uneventful epidural or brachial plexus block, Bup concentrations seldom exceed 1 - 1.5 µg/ml (2). But, the threshold for the cardiac toxic effects of Bup might be lowered by other concurrently administered drugs which exert depressant effects on the myocardium. Such drugs are frequently administered to surgical patients, yet they are not always taken into account by the anesthesiologist. The aim of this study was to investigate the possible role of drug interactions in precipitating cardiac accidents during regional anesthesia.

Methods. The experiments were performed in 30 dogs, anesthetized with thiopental (4 mg/kg) and chloralose (80 mg/kg), artificially ventilated to keep constant, near normal, arterial blood gas tensions and pH, and warmed to prevent hypothermia. Mean arterial blood pressure was continuously recorded, as well as duration of the QRS complexes by EKG. Right ventricular conduction time (CT) was determined using two endocavitary electrodes, one advanced to the apex, and the other, the pacing electrode, placed near the base. In view of the rate-dependency of conduction disorders, the pacing rate was high, 180/min. Effective refractory period (ERP) was measured by the extra-stimulus method (3).

In all animals, Bup was infused i.v. at an average dose of 0.1 mg/kg/min, after a 4 mg/kg loading dose, to produce a prolongation of CT by more than 50 %. Plasma Bup concentrations (measured by HPLC) required to achieve this ranged from 2 to 3.5 µg/ml. After maintaining stability of this preparation for 50 - 60 min, dogs received moderate i.v. doses of one of the following drugs : cibenzoline (3.0 mg/kg), disopyramide (2.0 mg/kg), propranolol (0.3 mg/kg), clomipramine (0.5 mg/kg/min over 20 min), and verapamil (0.3 mg/kg) [n = 6 in each group].

A paired Student's t test was used to compare values obtained with simultaneous administration of Bup and another drug to values with Bup alone.

Results. The prolongation of CT and widening of QRS complexes caused by Bup were enhanced by the first three drugs. Cibenzoline increased CT from 54 ± 5 (mean ± SEM) to 76 ± 6 ms ($p < 0.001$), disopyramide from 55 ± 4 to 72 ± 4 ms($p < 0.001$), and propranolol from 47 ± 2 to 72 ± 5 ms ($p < 0.001$). The QRS complexes were prolonged from 77 ± 2 to 100 ± 2 ms, 76 ± 3 to 90 ± 5 ms, and 76 ± 3 to 87 ± 3 ms ($p < 0.001$) with the three drugs, respectively. These alterations were not caused by significant decreases in blood pressure, which might have increased Bup concentrations by decreasing its clearance. Plasma Bup concentrations remained at control values throughout the experiment.

Since the increase in conduction disorders with cibenzoline and disopyramide were not accompanied by a significant increase in ERP, reentrant arrhytmias were likely consequences. In fact, ventricular tachycardia and even fibrillation did occur when prolongation of CT exceeded 100 %.

In contrast to the above, clomipramine in therapeutic doses appeared to lengthen CT and widen the QRS only moderately (less than 20 %). Verapamil was entirely devoid of effect on ventricular conduction.

Discussion. Potentiation of Bup-induced conduction disorders by a class IC antiarrhythmic drug such as cibenzoline might have been predicted in view of its selective blockade of fast sodium channels. Although these channels are affected to a lesser degree by class IA antiarrhythmic drugs such as disopyramide, effects on conduction by this group of drugs is not surprising. The mechanism of action of propranolol in this circumstance probably relates to inhibition of adenylcyclase and reduction in sodium extrusion. Our results suggest that clomipramine exerts a significant depressant effect on ventricular conduction only at near toxic doses. Finally, verapamil, a calcium channel inhibitor, could not be expected to potentiate disorders resulting from fast sodium channel block.

A possible recent administration of cibenzoline, disopyramide or propranolol must be systematically investigated before locoregional anesthesia with Bup, as the association in sufficient doses is likely to lead to serious conduction disorders and dysrhythmias.

References

1. Béal J.L., Freysz M., Timour Q. et al. : Haemodynamic effects of high plasma concentrations of bupivacaine in the dog. Eur. J. Anaesth., in press.

2. Timour Q., Freysz M., Lang J. et al. : Electrophysiological study in the dog of the risk of cardiac toxicity of bupivacaine. Arch. Int. Pharmacodyn. 287, 65-77, 1987.

3. Wit A.L., Weiss M.B., Berkowitz W.D. et al. : Pattern of atrioventricular conduction in the human heart. Circ. Res. 27, 345-359, 1970.