Title: ISOFLURANE STOPS REFRACTORY SEIZURES

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Introduction: General anesthesia has been recommended when status epilepticus is refractory to conventional anticonvulsant therapy(1). Halothane has been recommended but without experimental justification(1). Isoflurane, because of its effect in producing electrographic suppression should be the best of the presently available inhaled agents to use. We assessed the efficacy, safety and logistics of isoflurane administered to six patients with refractory status epilepticus. In addition, we assessed the efficacy of isoflurane administered to rats with flurothyl-induced status epilepticus.

Methods: Human Study. Isoflurane anesthesia was given to 6 patients, 2-30 y.o. (two previously reported(2,3)) in 5 institutions. Each patient was first demonstrated to have continuous seizure activity despite treatment with, at least, phenytoin, phenobarbital, and diazepam (or lorazapam). The etiologies of the seizures were: idiopathic (2 patients), viral encephalitis (2 patients), organophosphate insecticide ingestion, and arteriovenous malformation. Each was endotracheally intubated prior to isoflurane administration. Isoflurane was administered to each patient starting at 0.5-1% inspired concentration, subsequently being increased gradually as indicated by seizure activity and as hemodynamically tolerated.

Rat Study. Nine Long-Evans Rats, 300-400 grams were fed ad lib. Anesthesia was induced in 3-4% halothane in O2 followed by vecuronium 4 mg IP, endotracheal intubation, and mechanical ventilation. Rectal temperature, intra-arterial pressure, and EEG were monitored. Halothane was discontinued for 30-45 min, during which time, atropine .1mg SQ, followed by .02 mg IV was given. Vecuronium 4mg IV was given at the onset of flurothyl administration. Flurothyl was administered via vaporizer with .5% increments in vaporizer settings qlmin up to 3%. After 40 minutes of flurothyl-induced seizures, isoflurane was started and increased .5% q1-2min up to 2% inspired. A phenylephrine IV infusion was used to maintain MAP>100 mmHg. Flurothyl was continued for another 60 min with isoflurane being continued for a total of 90 min.

Results: Human Study. Isoflurane produced cessation of seizures with a burst suppression pattern > 30 sec (see figure) at inspired isoflurane concentrations ranging from 0.5 to 3.0% (end-tidal .3-.8% in 3 patients) and was able to be titrated to produce a burst-suppression pattern on EEG. Durations of isoflurane administration were 1, 5, 36, 45, 48, and 54 hours, (the one-hour case received concomitant N20). Blood pressure support was required in all patients with IV phenylephrine, dopamine, and/or fluid infusion. Significant hypotension and bradycardia occurred in none of the patients. In the 4 undergoing prolonged anesthesia average MAP was 60-70mmHg. Two patients had PA catheters placed (both 13 y.o.). During isoflurane the following occurred in these patients: mean PAP 19-25mmHg, PCWP 12-13mmHg, and CO 4.7-7.1 L/min. When isoflurane was discontinued, seizures resumed in 3 patients, 2 of whom subsequently expired; and did not recur in 3 patients of whom one (organophosphate) expired 12 hours later with the abrupt onset of systemic hypertension and electrographic silence, one expired eight weeks later of encephalopathy and multiple organ failure and one (viral encephalitis) gradually regained consciousness with a residual partial cognitive deficit. Rat Study. Isoflurane administration stopped seizures in all rats.

Discussion: Which general anesthetic (intravenous or inhaled) is optimal in the treatment of refractory seizures cannot be stated presently with certainty. The ample clinical experience which exists with the use of intravenous general anesthetic anticonvulsants suggests that, presently, intravenous agents should be used initially. When, however, they are ineffective, not tolerated, or physical dependence is suspected (producing seizures on withdrawal) inhaled anesthesia with isoflurane should be considered. Based on our experience with these six patients, and preliminary data in rats, we suggest that: 1) Isoflurane is an effective, rapidly titratable anticonvulsant: 2) The seizure threshhold can be quantitated by noting the isoflurane concentration required to effect a given degree of electrographic burst suppression; 3) Prolonged isoflurane anesthesia is hemodynamically tolerated; and 4) Prolonged isoflurane anesthesia can be given outside the operating room.

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