Doxapram Hydrochloride[1] in Hemorrhagic Hypotension (35522)

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Definitive studies in laboratory animals have shown that doxapram HCl is a rather specific and potent stimulant of the brain stem (1, 2). The net result of this action is manifested in several pharmacologic effects, of which an increase in respiratory function and an elevation in arterial blood pressure are the most prominent [(3), unpublished results]. In view of profound effects in normovolemic dogs, the present study was conducted to determine if doxapram HCl treatment would influence survival in dogs that were subjected to profound hemorrhagic hypotension, possibly "irreversible" hemorrhagic shock.

Methods. Forty mongrel dogs of either sex, weighing between 7 and 14.5 kg, were used. They were anesthetized with intravenous pentobarbital sodium, 30 mg/kg, and were run in pairs, *i.e.*, a treated and a control in each experiment. An ink-writing kymograph was used for recording femoral arterial blood pressure. An endotracheal tube was employed to insure a patent respiratory airway. Cannulas connected a femoral artery and vein to the arms of a Y-tube; the base branch of the tube led to a bottle in which shed blood was collected. This arrangement permitted arterial hemorrhage and venous reinfusion.

After the control blood pressure was recorded, each dog was bled into the reservoir until the mean arterial pressure reached 33 to 44 mm Hg (40 mm Hg in 34 of 40 dogs). The rate of bleeding and the blood pressure were controlled by adjusting the height of the reservoir. When the blood pressure had stabilized at the low level, 20 mg/kg of doxapram HCl was given intravenously to the treated dog and an equivalent volume of saline was given to the control. At this point, the line to the reservoir of the doxapram-treated dog was closed to prevent further blood loss during the pressor action of doxapram HCl. The reservoir line in every preparation (including the saline treated) was checked frequently; it was left open when blood no longer flowed from dog to bottle. Blood pressure was recorded for 4 hr after treatment, and if the animals were living, blood remaining in the reservoir was reinfused (under pressure, if necessary), and the pressure was followed for an additional hour. Incisions were then closed and the animal was returned to its cage. Food and water were allowed *ad libitum*. Animals alive after 48 hr were considered as having survived the stress of the experimental procedure.

Results. The results summarized in Table I show comparable values in control and treated groups with regard to animal size and to treatment parameters. The only exception was the difference in the time between bleeding and treatment which statistically was barely significant. This difference was caused by two control values (142 and 179 min) that were produced in early experiments when technical difficulties were experienced in stabilizing blood pressure at the hypotensive level. Without these high values the stabilization time with standard deviation was reduced to 38.9 $\pm$ 16.7. The difference between groups was then not significant at the 95% level.

In most dogs, injection of doxapram HCl caused an immediate transient fall in blood pressure of 5 to 15 mm Hg. This was followed in 19 of 20 dogs by a pronounced rise to near the prehemorrhagic level where the pressure invariably remained, at least until this phase of the experiment was completed with reinfusion of blood remaining in the reservoir. It is not known why doxapram

[1] 3,3-Diphenyl-1-ethyl-4-(β-morpholinoethyl)-2-pyrrolidinone hydrochloride monohydrate; AHR-619; Dopram, Dopram-V, A. H. Robins Co.

TABLE I. Doxapram HCl in Severe Hemorrhagic Hypotension in Dogs.

	Mean ± SD		
	Controls	Treated	p value[a]
No. of animals	20	20	—
Body wt (kg)	11.4 ± 2.0	11.7 ± 1.4	> 0.5
Blood vol (ml)[c]	911 ± 157	939 ± 110	> 0.5
Hemorrhage			
Vol (ml)	469 ± 103	517 ± 75.6	0.1
Percent	51.8 ± 6.9	54.7 ± 7.5	> 0.2
Duration (min)	21.6 ± 18.7	14.5 ± 11.2	> 0.1
BP stabilization time (min)[d]	51.1 ± 46.2	27.0 ± 16.7	< 0.05
Mean arterial BP (mm Hg)			
Prehemorrhage	115 ± 18.2	124 ± 20.5	> 0.1
At max. hypotension[e]	39.4 ± 1.9	39.5 ± 1.7	> 0.5
Postdoxapram (min)			
15	47.9 ± 11.1	89.4 ± 19.0	< 0.001
60	52.7 ± 23.9	90.1 ± 25.2	< 0.001
240	60.2 ± 24.1	97.3 ± 25.3	< 0.001
Postreinfusion, 1 hr	87.5 ± 33.2	133 ± 29.6	< 0.001
No. deaths/no. survivors	14/6	2/18	< 0.05[b]

Tests for significance: [a] Student's t; [b] χ^2.

[c] Estimated as 8% of body weight.

[d] Time between reaching maximum hypotension and doxapram HCl (or saline) treatment.

[e] Level at which pressure stabilized after hemorrhage.

HCl did not elevate blood pressure in the remaining dog which eventually died.

Respiration was stimulated in all doxapram HCl-treated dogs, but the grossly observable increase was of relatively short duration when compared to normovolemic dogs run previously in this laboratory. Signs of awakening (blinking of the eyes, movement of the extremities and gagging on the endotracheal tube) were seen frequently. It was necessary to give supplements of the anesthetic to many treated dogs at this point.

During observation of survivors, it was noted that the doxapram HCl-treated dogs appeared essentially recovered within 24 hr, and that they were in better physical condition than the control survivors after 48 hr. They were more alert, moved about in the cage, and readily accepted food and water. The controls experienced considerable diarrhea and were extremely weak and listless.

Discussion. The data in Table I show essentially no difference between treated and control groups insofar as body weight and degree of hemorrhage are concerned. This is not meant to infer that the individual dogs within the groups were subjected to a comparable degree of shock stress. In this study (as in similar studies) the intensity of the shock state could not be determined. However, it was hoped that by making every effort to duplicate conditions in 20 paired experiments, the variability between treated and control groups was reduced substantially.

In addition to pretreatment similarities between groups, the results show also striking contrasts between groups following treatment. According to the statistical methods employed, differences in blood pressure and survival values were highly significant. And as already mentioned, there was a marked difference in appearance and in spontaneous activity between survivors in the respective groups. These results constitute striking evidence that doxapram HCl treatment had a beneficial effect in the animals subjected to severe hemorrhagic hypotension. And since symptomology among control survivors was highly indicative of "irreversible" hemorrhagic shock, there exists the possibility that dox-

apram HCl treatment might have decreased or even prevented those changes to which the shocked animal invariably succumbs.

The precise mechanism by which doxapram HCl influences survival in this experimental situtation is not known. This agent causes generalized sympathoadrenal discharge (3), which was presumably implicated in the restoration of blood pressure, improved respiratory function, and the excellent survival rate among doxapram HCl-treated dogs in the present study. If this were indeed the only mechanism involved, then these results are in general disagreement with the proposed use of vasodilating rather than vasopressor agents in hypovolemic hypotensive states. But doxapram HCl differs from most vasopressor drugs in that it has a marked, positive, and direct influence on respiratory function. The net effect of this difference may mean improved oxygenation of tissues, particularly those which cannot tolerate prolonged deficits in oxygen supply.

Summary. Mongrel dogs were anesthetized and bled until mean arterial blood pressure was reduced to about 40 mm Hg. After the blood pressure had stabilized at this level, doxapram HCl (20 mg/kg) or an equivalent volume of saline was given intravenously. Experiments were always conducted in pairs, with one dog for each treatment. In animals given doxapram HCl, there was a prompt increase in arterial blood pressure and respiratory function while essentially no favorable change was seen following injection of saline in control animals. Also, doxapram HCl-treated dogs recovered quickly and this group showed a 90% survival rate as compared to 30% in the controls. These results are interpreted as indicative of beneficial effects of doxapram HCl in experimental hemorrhagic hypotension.

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