Dimethyl sulfoxide in the treatment of experimental brain compression

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✓ Forty rhesus monkeys were subjected to acute experimental head injury by extradural balloon compression of the brain. A critical endpoint in the compression was used to inject either saline, urea, or dimethyl sulfoxide (DMSO). All saline-treated animals died. Ten of 15 urea-treated animals survived, while 14 of 15 DMSO-injected monkeys survived. The incidence of neurological deficits seen in survivors was four for urea and one for DMSO. It is concluded that DMSO is capable of modifying the mortality rate and posttraumatic sequelae of brain injury in the experimental model used.

KEY WORDS · dimethyl sulfoxide · experimental brain compression · urea

EXPERIMENTAL brain injury can be produced in a variety of ways. For this study, we used the acute extradural compression model with which this laboratory has been familiar for many years.[15,20]

A number of drugs now exist that modify the effects of some head injuries, among which urea is often used. In selecting urea for our treated models we are aware that other ancillary drugs are available that could serve as well, or in some cases better, than this osmotic agent. It seems clear that whatever physiological factors are to be tested, it is first necessary to create a reproducible and predictable animal model before a pharmacological agent can be properly evaluated.

Dimethyl sulfoxide (DMSO) was chosen as a possible therapeutic agent in experimental head injury because it protects a variety of cells from mechanical damage[3] and acts as an antiinflammatory and diuretic agent with a resulting reduction of edema.[9,10] DMSO is a dipolar aprotic solvent, which has been shown to cross the dermal barrier rapidly in high concentrations with little or no permanent tissue damage.[16] It has also been shown to cross the blood-brain barrier to assist in the penetration of certain compounds. such as ^{14}C-pemoline,[4] L-dopa,[5] and adrenaline and noradrenaline.[14] At first we did not know whether penetration of DMSO through the blood-brain barrier would be desirable or result in a disadvantage for the purpose of our study.

Methods and Materials

Forty macaque (Macaca mulatta) monkeys of mixed sex and weighing 3.4 to 4.5 kg were divided at random into three groups as follows: 10 were treated with 20 cc of normal saline, 15 with 10 cc of urea (3.2 gm) followed by 10 cc of normal saline, and 15 with approximately 10 cc of pure DMSO mixed with 10 cc of normal saline (2.2 gm/kg). Animals were anesthetized intraperitoneally with sodium pentobarbital, 40 mg/kg, and the head fixed in a stereotaxic apparatus (Fig. 1). Brain injury was induced by supra-

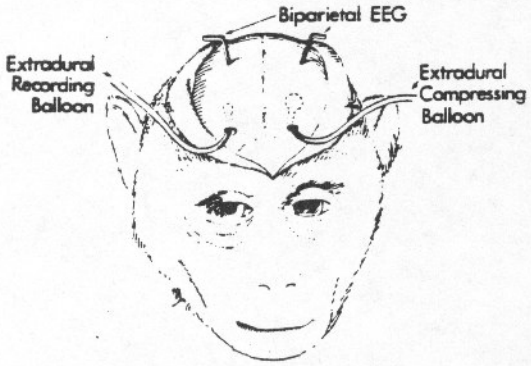

FIG. 1. Experimental set-up showing monkey placed in a stereotaxic headholder. Bifrontal burr holes are made for recording intracranial pressure and for extradural compressing balloon. Biparietal leads are screwed into skull in contact with the dura for EEG recordings. Pial window may be placed contralateral to the compressing balloon.

tentorial extradural compression with a 5 mm Happenstein balloon attached to a rubber catheter, and introduced into the left parietal area. The balloon was then slowly filled with an initial 0.6 cc of saline, mixed with a blue dye indicator (for detecting leaks in the system, none of which occurred) and thereafter, 0.2 cc increments were added for every 5 min. The total mean volumes of compression for the three groups are summarized in Table 1.

A Beckman Type R dynograph was used to record respiration, systemic arterial pressure, left carotid blood flow, intracranial pressure, and EEG. Respiration was monitored by a Harvard pneumotachygraph connected to a Statham strain gauge. All animals were intubated and allowed to breathe spontaneously. Minute volumes were measured with a Monoghan Respiratory Ventilation meter. Femoral catheterization was used for intravenous fluid administration and to record systemic arterial pressure. Left carotid blood flow (Lt. Car. B.F.) was recorded with a 6 mm calibrated flow probe on the common carotid with the external carotid ligated in continuity. The flow probe was connected to a square wave electromagnetic flowmeter* and pulses were registered on the dynograph. Zero flow was recorded after 2-sec occlusion of the common carotid proximal to the flow probe. A recording balloon with a polyethylene tube attached to a Statham strain gauge was placed on the right parietal area to measure intracranial pressure. Parietal EEG unipolar electrodes were screwed into the skull bilaterally 1 cm from the midline and 1 cm posterior to the coronal suture. Acrylic dental cement was used to seal the bifrontal burr holes made for the recording and compression balloons. Dura was removed over a pial window placed contralateral to the compression balloon in the monkeys to study and microphotograph the pial vasculature at low power magnification (50×) during the surgical procedure. The window was held in place with acrylic dental cement.

Plasma volumes were determined using commercially available RIHSA† according to the method of Albert.[2] Determinations were made at two points during the course of the experiment: before the initiation of extradural compression and after injection of DMSO or urea. IHSA-I^{125} was used for the first determination and IHSA-I^{131} for the second, because of the difference in photopeak energies. Background samples and post-drug-injection samples at 10, 20 and 30 min were obtained in order to extrapolate to zero time. Determinations were not made for the saline-treated animals because of their failure to survive with reasonably normal circulatory dynamics for a sufficient time interval after the period of apnea.

During compression, physiological changes were observed in all 40 monkeys

* Flowmeter provided by Carolina Medical Electronics, Inc., King, North Carolina 27021.

† "Albumotope" made by E. R. Squibb and Sons, Inc., Princeton, New Jersey 08540.

TABLE 1

*Mortality rate in 40 rhesus monkeys subjected to extradural balloon compression**

Group	No.	Survivors	Mortality (%)
saline-treated	10	0	100
urea-treated	15	10	33
DMSO-treated	15	14	7

* Average balloon compression volume required to reach critical apneic point (endpoint) was 5.1, 5.0, and 5.5 cc for saline, urea, and DMSO-treated groups respectively. Mean balloon compression volume for all animals was 5.2 cc.

which were similar to those previously reported from this laboratory using cats[15] and dogs.[20] At the stage of apnea, the animals showed fixed, dilated pupils, a bilaterally flat EEG, a self-sustaining rise in intracranial pressure and blood pressure (as described by Langfitt, *et al.*,[18]) and a reduced blood flow as measured by the carotid flow probe and as seen through the cortical window. Following the period of total respiratory cessation, apnea was arbitrarily allowed to extend to a minimum of 45 sec. A few respiratory gasps followed and the drug under trial was administered to coincide with the first respiratory spike (Figs. 2–4, *arrow*). The period of apnea was therefore variable beyond 45 sec but the subsequent respiratory gasp was present in all animals. The balloon was decompressed 1 hour later in the survivors.

Saline, urea, and DMSO were infused at the rate of 8 cc/min at room temperature. After the surgical procedure, the surviving animals were injected intramuscularly with 100 mg Steclin and the scalp suture wound was covered with Terra-Cortril ointment. The brains from eight urea- and DMSO-treated animals were used to measure the percent difference of dry/wet weight ratio, 24 and 48 hours after compression.

Results

Survival

In Group 1 (saline only), all 10 control animals died; only one survived the posttrau-

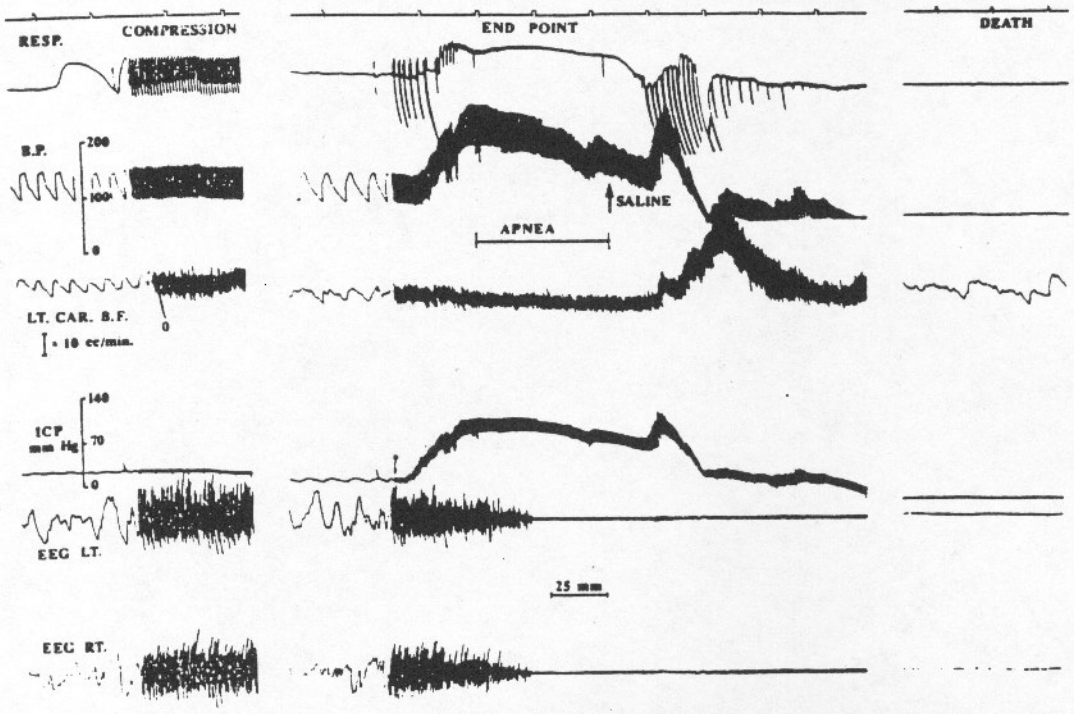

FIG. 2. Three bands of polygraph recordings measuring physiological parameters during extradural balloon compression, endpoint, and stabilization or death. During compression, no remarkable changes are seen. At endpoint, respiration (Resp.) shows high amplitude slow wave activity culminating in a variable period of apnea. Following apnea, a spontaneous respiratory gasp is seen (*arrow*) and the drug or saline is injected. Prior to the apneic period, a rise in systemic arterial pressure (BP) is evident, accompanied by a sustained rise in intracranial pressure (ICP). The last 0.2 cc of fluid increment in the extradural balloon is marked by a *circled arrow*. Left carotid blood flow (LT. CAR. B.F.) is not measurable during endpoint. Left and right parietal EEG is seen flattening during apnea. After urea or DMSO is injected, ICP falls suddenly with urea and more gradually with DMSO, while the drop after saline is only partial. Stabilization of all parameters was seen in the surviving animals 8 to 10 min following the endpoint except after saline injection where 9 of 10 monkeys died before balloon compression (10th monkey died within 10 hours after surgery). Time markers are 25 mm/min and 25 mm/sec for fast tracings.

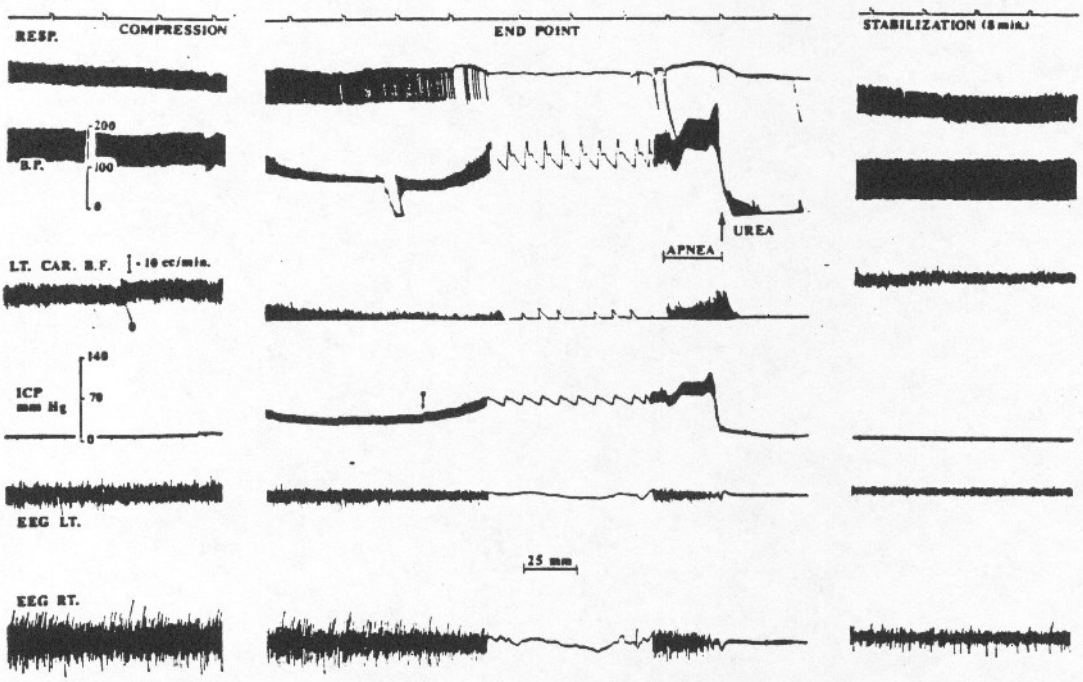

FIG. 3. Three bands of polygraph recordings measuring physiological parameters during extradural balloon compression, endpoint, and stabilization or death. (See Fig. 2 for detailed explanation.)

matic period, and even this animal did not live for more than 10 hours. In Group 2 (urea plus saline), 10 of the 15 monkeys survived; of these, four had various neurological abnormalities (Table 2) and six recovered uneventfully from surgery and were adjudged grossly normal in every respect. All five deaths occurred before decompression. In Group 3 (DMSO-treated) 14 of 15 monkeys survived. Postoperatively one animal showed a mild neurological defect, consisting of transient right-sided paresis of the hand and arm. Motor and sensory function as well as alert, aggressive behavior were rated normal in all Group 3 monkeys following recovery from anesthesia. The only death in this group occurred shortly after decompression even though the functional parameters had seemed to be well stabilized up to that point.

A 16th monkey that recovered after DMSO treatment is not included in this series because it was artificially ventilated after being presumably dead; nevertheless, this animal should be reported since it recovered with no apparent neurological deficit after undergoing 6½ minutes of apnea and 12 minutes with a flat EEG.

Blood Volumes

A significant mean increase over control levels was similar for both agents: 18.5% in the case of urea, and 22.5% in the case of DMSO. DMSO and urea are both known to produce diuresis[10] which would tend to minimize this increase in plasma volume.[2] This suggests that following the endpoint of compression and injection of the therapeutic agent, there may have been an even greater increase in plasma volume than we were able to detect.

A beneficial hemodilutional effect with decrease in blood viscosity and improved cerebral blood flow is implied by the increase in

TABLE 2

Gross and neurological deficits in urea- and DMSO-treated monkeys 24 hours after compression

Deficit	Urea (4 monkeys)	DMSO (1 monkey)
lethargy	3	0
anisocoric pupils	3	0
paresis (right side)	2	1
lack aggression	4	0

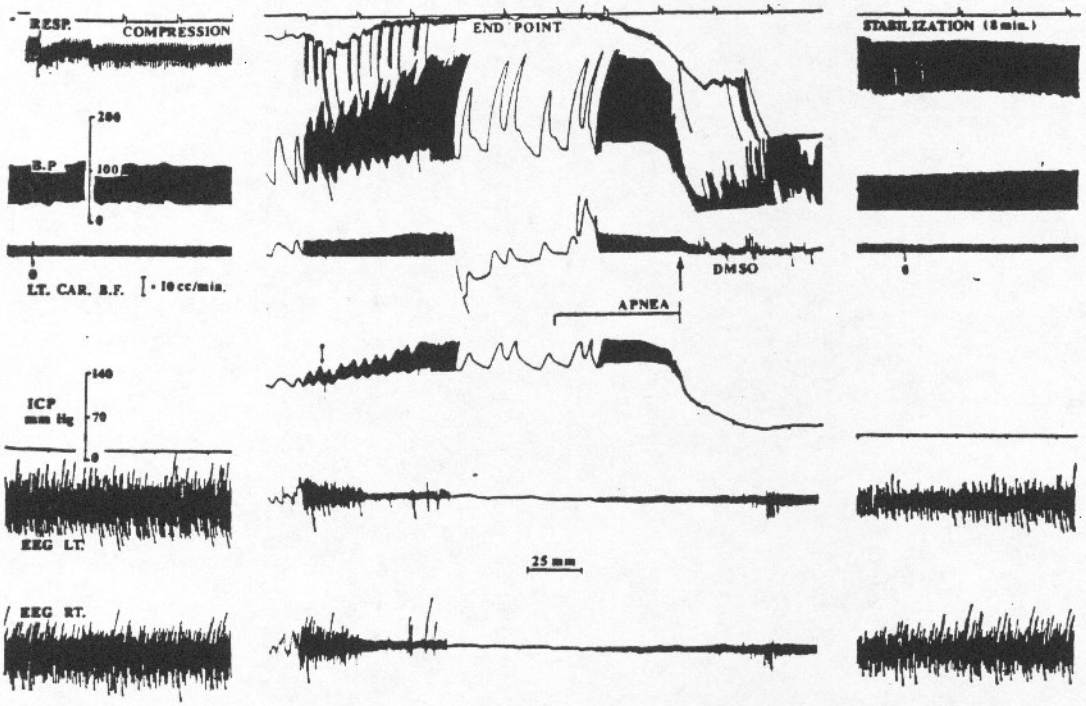

FIG. 4. Three bands of polygraph recordings measuring physiological parameters during extradural balloon compression, endpoint, and stabilization or death. (See Fig. 2 for detailed explanation.)

plasma volume. One cannot be certain that this was due to the therapeutic agents exclusive of other experimental factors, because the insufficient survival time of the control animals precluded postcompression blood volume determinations.

Endpoint Observations

During and after the critical endpoint, the following observations were made.

Respiration. In half of the control animals, respiration returned to a regular pattern following injection of saline but within an hour began failing and finally stopped; in the remaining animals in this group, only a few respiratory spikes were recorded, followed quickly by death.

Respiration in monkeys treated with urea or DMSO stabilized a few minutes after injection and remained stable in the survivors throughout recovery. It appeared that the respiratory amplitude was greater after DMSO (Fig. 4), suggesting a stimulatory effect of this agent on respiration.

Systemic Arterial Pressure. Animals treated with saline showed an initial improvement in the arterial pressure. This improvement coincided with the respiratory gain observed in half of these animals. The arterial pressure, however, deteriorated within the hour and finally dropped to zero. In urea- and DMSO-treated monkeys, the arterial pressure returned to baseline levels within 10 min after the endpoint and remained normal in the survivors.

Left Carotid Blood Flow. Left carotid blood flow decreased in all animals in relation to the increasing fluid levels in the compressing balloon. The flow was barely measurable during apnea, but quickly returned to normal levels coinciding with stabilization of systemic arterial pressure and respiration in animals which survived.

Intracranial Pressure. Following saline injection, intracranial pressure (ICP) decreased from its peak level to about a level 50% to 30% above the baseline and remained elevated until death (Fig. 2). After injection with urea, the ICP dropped quickly to baseline. Following DMSO, ICP also dropped to baseline levels but more gradually (Figs. 3 and 4).

Electroencephalography. Electrical activity in the saline controls was variable

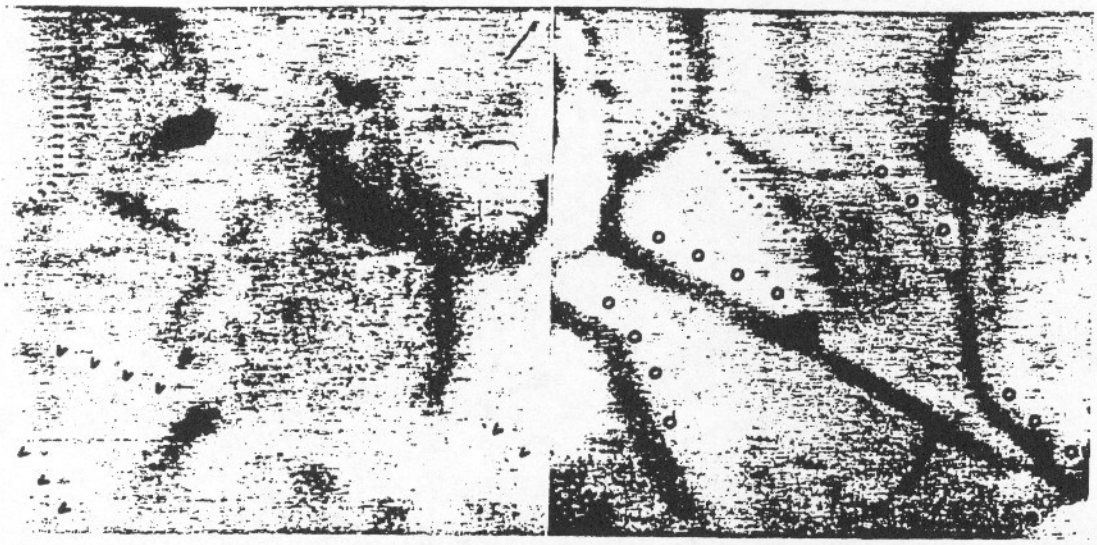

FIG. 5. *Left:* Pial vessels during apneic endpoint as seen through the cranial window. Large avascular areas are seen in cortex while vessels are barely discernible due to arrest (*v marks*) or severe reduction of blood flow caused by contralateral balloon compression. *Right:* Pial blood flow 30 to 60 min after DMSO returns to almost complete revascularization as evidenced by the return of vessels (*o marks*) where prior arrest of blood flow had occurred. *Double and single rows of dots* indicate the orientation of both cortical fields. Balloon compression was maintained for an hour after drug treatment. × 50.

(Fig. 2). Some monkeys in this group regained reasonable EEG amplitude following endpoint compressions, while others showed low-amplitude, fast-wave activity which continued until death. Quasi-normal EEG activity was regained some 5 to 20 min after either urea or DMSO treatment in the survivors (Figs. 3 and 4).

Cortical Blood Flow. During the apneic period, the circulation was virtually stopped in all animals and microemboli were observed (Fig. 5, *left*). Saline injection did not significantly modify the rapidly deteriorating circulation after apnea. Following urea or DMSO injection, the rate of flow gradually increased until nearly all channels under microscopic examination gained practically normal revascularization (Fig. 5, *right*). Small vessel branches which had been virtually abolished by the compression were seen to return within 30 to 60 min in the urea- or DMSO-treated survivors.

Pupils. Reduction of pupillary size was not seen in any of the 10 monkeys treated with saline including one that survived 10 hours. The mydriatic pupils were reduced to precompression size in all DMSO-treated monkeys including the animal that later succumbed after decompression. Six of the urea survivors adjudged grossly normal after surgery had pupillary responses similar to those with DMSO. Three other urea-treated monkeys showed anisocoric pupils (Table 2) even after surgical recovery, while a fourth had partial mydriasis but light-reactive pupils.

Fasciculation. About 1 min following the DMSO injection, a brief fasciculation of the monkey's body and limbs was observed. The tremors were as characteristic as the strong odor of garlic noted in the monkey's breath soon after DMSO.

Balloon Decompression. Decompression of the extradural balloon 1 hour after the drugs were injected was not marked by any significant changes in the physiological responses measured.

Urine Volume. Copious volumes of urine were generally excreted within 1 hour after injection of urea or DMSO. The urine in the DMSO monkeys was coffee-colored due to the presence of methemoglobin and hemoglobin.[7] No blood cells were found in the urine of these animals even after centrifugation.

Brain Weights. The percent difference of dry/wet brain weights taken 24 and 48 hours after compression indicated no increased fluid accumulation in any of the survivors examined. Survivors had a mean dry

/wet brain weight ratio of 23.2% (control values, % of wet weight: 23.3 ± 2%) in either hemisphere after 24 or 48 hours.

Discussion

The protective effects of DMSO as compared to urea- or saline-treated monkeys is shown in Tables 1 and 2. Animals treated with DMSO recover within a few minutes and return to stable physiologic homeostasis within approximately 10 minutes following the end point. At this time respiration, systemic arterial pressure, intracranial pressure, blood flow, and EEG return to normal levels, while the fixed, dilated pupils are reduced to precompression size. Stabilization after urea basically follows the same pattern as with DMSO. However, the period of recovery in four of the 10 surviving animals was marked by lethargy, anisocoric pupils, loss of aggression, and, in one case, hemiparesis (Table 2). No gross neurological signs were noted in the DMSO survivors, except for one animal that showed mild and transient right-sided paresis in the arm and hand.

Respiration

Whatever activity DMSO had in the animal after intravenous administration was quite rapid since arterial and intracranial pressures were quickly lowered, while respiration was stable within a few minutes. This suggests that DMSO either induces rapid diuresis or increases respiration by stimulation of neural respiratory receptors. In support of this suggestion, we observed that in normal anesthetized rhesus monkeys, 2 gm/kg of DMSO in a 50% solution injected intravenously increased the respiratory minute volume on the average by 95%. The minute volume remained high for 20 min then sloped slowly to control values. This effect of DMSO on respiration lasted for about 90 min. Urea did not appear to influence the respiratory minute volume under similar conditions. Figures 3 and 4 show the relative increase in respiratory amplitude after DMSO both in relation to its preinjection amplitude and to the respiratory pattern following urea administration.

Species Differences

Two studies,[7,22] both using cats, have reported that an intravenous injection of 200 mg/kg of DMSO produced apnea and a transient fall in blood pressure. Our own results in monkeys do not support these findings. The discrepancy could be due to species difference and also to the fact that the LD_{50} of DMSO in cats appears to be much higher than in monkeys. An experimental model for compression similar to the one described for the monkeys was attempted in the cat but later abandoned due to this difficulty. Doses of DMSO ranging from 50 to 500 mg/kg in sodium-pentobarbital-anesthetized cats proved so toxic that a reproduceable brain injury model could not be evolved.

Anoxia

The pharmacological versatility of DMSO makes it difficult to explain its apparent protective role in brain compression. Finney, *et al.*,[8] showed that a 10% solution of DMSO with or without hydrogen peroxide protects against experimental cardiac ischemia, possibly by aiding in the diffusion of oxygen into the myocardial tissue, thus affording a higher degree of protection from anoxia as compared to control models. Another report[11] demonstrated a dose-related ratio showing that as the concentration of DMSO is increased, oxygen consumption in the frog skin is reduced. These investigators also observed that the depression of the oxygen consumption could be reversed with no permanent tissue damage when DMSO was later removed with Ringer's solution.

Radiation Protective Effect

Ashwood-Smith[3] has reviewed the radioprotective properties of DMSO when animals are exposed to a lethal dose of x-rays (LD_{99} 1007 rad). It appears that the protective mechanism is functional at the cellular level[3] and may involve cellular increased resistance to anoxic damage. Thus, van der Meer[26] showed that the oxygen tension in the spleen was reduced after DMSO. This could result in less oxygen utilization by the cells and hence lower the degree of damage produced by anoxia in DMSO-treated animals. Moreover, unpublished preliminary experiments from this laboratory show that prior intraperitoneal administration of 3.5 gm/kg of a 50% DMSO solution protects rats

(paired with saline controls) from death when the animals are subjected to hypoxic hypoxia in a nitrogen chamber. This protection against anoxia could conceivably explain why (but now how) one DMSO-treated monkey (No. 16) recovered uneventfully after a 6½ minute period of apnea and an isoelectric EEG for 12 minutes.

Blood Flow

Previous experiments in this laboratory[15,20] have shown that after acute head injury induced by balloon compression, carotid and cortical cerebral blood flow will fail and the animal will die of respiratory arrest. Preceding this period of circulatory failure, sludging of erythrocytes and platelets occurs which obstructs the regional vascular supply, thus decreasing oxygen transport. Hemodilution[20,24] is thought to benefit cerebral circulation by decreasing vascular resistance and increasing perfusion. This could result in lowering the incidence of platelet and red cell aggregation at the cerebrocapillary level. In addition to the intracapillary agglutination of red cells and decreased oxygenation, dilatation of available vascular channels may occur. In certain experimental models, both *in vitro* and *in vivo*, DMSO has been shown to lessen the adhesiveness[6] and aggregation[12] of platelets as well as thrombus formation. The effect of DMSO on blood flow was reported by Adamson, *et al.*,[1] who applied DMSO to a pedicle flap raised on the back of rats and observed that slough was decreased by 70% and pedicle flap blood flow markedly increased.

Intracranial Pressure

In our compression model, a high intracranial pressure was achieved at the point of apnea which could be lowered to baseline levels with urea or DMSO. The drop of intracranial pressure after urea was somewhat more rapid than after DMSO (Figs. 3 and 4). Even after saline injection, there was about a 50% drop in intracranial pressure which persisted until the monkey died. It is still undetermined, however, whether the intracranial pressure drop after saline is due to some hemodilution effect of this physiological fluid or rather is a consequence of the spontaneous respiratory movements which are evident following endpoint.

Diuretic and Antiedema Effects

DMSO has been shown to be a potent diuretic agent. Formanek and Suckert[10] reported that a 90% solution of DMSO applied topically to rats five times daily increased the urine volume tenfold, with a concomitant increase in sodium and potassium excretion. Formanek and Kovacs[9] showed that topically applied DMSO was capable of inhibiting traumatic edema induced by intrapedal injection of otologous blood in the rat leg. DMSO also reduced inflammatory edema induced by carrageenin.[13]

Cardiac Action

The action of DMSO in stabilizing the alteration of vital signs after cerebral balloon compression is unknown. It has been reported[21] that 10 gm of DMSO in a 25% solution with saline given intravenously to dogs will increase the cardiac rate concomitant with an increased electrical amplitude of the QRS complex and will also elevate the mean arterial pressure and the pulse pressure. At the same dose, the rate and depth of respiration increases from 10 to 32/min following DMSO.

Lysosome Activity

Sutton, *et al.*,[25] demonstrated that, following brain injury induced by a focal freezing lesion, a release of lysosomal enzymes appeared to contribute to the cellular necrosis and brain edema, and that this lysosomal effect could be minimized by stabilizing the membranes of these cytoplasmic organelles through hypothermia. This finding is also interesting because Weissman, *et al.*,[27] reported increased lysosome stabilization in the rabbit liver by the use of DMSO in conjunction with cortisone and chloroquine. It has not yet been determined, however, whether DMSO alone can stabilize lysosome disintegration after injury rather than by acting as a potentiator of cortisone. It is also known that DMSO lowers body temperature and can act as a hypothermic agent when injected into animals.[3]

Toxicity

The toxicity of DMSO in monkey appears to be relatively low. Mason[19] found that the maximum tolerated dose in monkeys injected daily with intravenous DMSO was 4

gm/kg for 69 days. The single dose LD_{50} in the same animal has been estimated to be between 4 and 8 gm/kg. Our own studies indicate that the normal rhesus monkey under light nembutal anesthesia will tolerate a single 7 gm/kg dose of pure DMSO with no gross functional alterations. Moreover, it has been observed that regardless of the route of administration or how high the dose, the signs and symptoms of toxicity in any animal given DMSO that survives for 24 hours will eventually disappear and that the most transitory effect of this substance is to be found in the central nervous system.[19] We have noted that three monkeys treated with DMSO in our experimental compression model and which have now been kept for 20 weeks, show no gross neurological or functional abnormalities since their surgical recovery.

Fasciculation

The skeletal muscle fasciculations observed in the experimental animals may result from an anticholinesterase activity by DMSO. This suggestion is supported by evidence showing that in *in vitro* assays, 8% DMSO will inhibit bovine erythrocyte cholinesterase 16% to 18%.[23] Cholinesterase inhibition would also explain the fasciculation of skeletal muscle.[17]

Conclusions

It is concluded from this investigation that DMSO is capable of significantly modifying the mortality rate in monkeys subjected to acute extradural balloon compression of the brain. Mortality after a critical endpoint was 100% in saline-treated controls as opposed to 7% in animals receiving a single intravenous dose of DMSO in solution. Similarly, compressed monkeys receiving urea had a mortality rate of 33%. In addition, neurological deficits seen in the surviving animals were less evident in DMSO-treated monkeys when compared with animals injected with urea.

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