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DIFFERENCE BETWEEN LETHAL DOSES OF TOXIC SUBSTANCES INJECTED INTRAVENOUSLY AND INTRA-ARTERIALLY

G. ROSENFELD and F. G. DE LANGLADA *

Laboratory of Hematology, Instituto Butantan, São Paulo, Brasil

According to Braier (1, 2), when a toxic hemolytic substance, such as benzene, is injected intravenously in rabbits, 0,12 ml/kg provoke hemolysis and death of the animal in a few minutes, whereas this dose can be increased five times in intra-arterial injection without producing such manifestations. This diversity in the threshold of the toxic dose is due to the retention of the injected substance in the region served by the artery, even if no interruption of venous efferent circulation is made. This fact can also be observed with chloroform, saponin or non-hemolytic toxics, such as strychnine sulphate, potassium chloride, potassium cyanide and sodic luminal (1, 2).

In this paper, a comparison between these two routes of administration was made, as regards the lethal potency on guinea-pigs of benzene, potassium cyanide and venom of *Bothrops jararaca*.

Material and methods

Guinea pigs were used. The animals were anesthetized intraperitoneally with nembutal with doses of 15 mg/kg. Median laparotomy was made and the injections were given in the abdominal aorta or in the distal cava vein. Animals thus treated, but not injected with toxics (controls) survived 48 hours. In the experiments with dogs, injections were given in the femoral vein or femoral artery without anesthetics or skin incision.

The criterion of observation time for death varied according to the drug or the kind of animal that had been used. In guinea pigs injected with benzene, potassium cyanide and snake venom (*Bothrops jararaca*), the observation time was restricted to 30 minutes for the two first mentioned substances, and 60 minutes for the last one; short times were selected because the animals were anesthetized and laparotomized and the action of the drugs with such doses was very rapid. Dogs injected with benzene were observed for 24 hours since they had not been submitted to any traumatic operation.

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Results

Intravenously injected benzene killed all guinea pigs from the dose of 0,2 ml/kg or higher, while intra-arterially the same results were observed only with doses 32 times higher, i.e., 6,4 ml/kg (Table 1): in dogs the intravenous doses of 0,2 ml/kg killed 3 animals in 3, 4, and 5 minutes respectively, surviving only one animal: intra-arterially the same dose killed only one animal in 80 minutes, having survived three of them (Table 2). For larger doses, mortality was the same in both kinds of injections, but survival times were markedly longer when doses until 0,8 ml/kg were injected arterially.

Potassium cyanide injected intravenously killed all guinea pigs with doses starting from 10 mg/kg, while the same effect appeared only with 20 mg/kg when injected intra-arterially (Table 1).

Snake venom of *Bothrops jararaca* injected intravenously, started killing all guinea-pigs with 1 mg/kg, whereas only the dose of 4 mg/kg produced the same effect when injected intra-arterially (Table 1).

Discussion

The intra-arterial route has been utilized in chemotherapy as the most direct route for obtaining high concentrations of the therapeutical agent at the tumour site, permitting even the intravenous use of higher doses than usually, as it had been reported by Byron, Singh, Bierman and Kelly (1959). The principle indicated by Braier (1, 2) however, is quite different: he demonstrated that doses not imaginable as possible, could be injected intra-arterially, based on the knowledge of the intravenous toxic dose.

Results reported in this paper completely confirmed Braier's affirmations (1960-1961) that to cause death by toxic substances, much higher doses are required by intra-arterial than by intravenous injections. Probably, the explanation of this fact is the retention or the better absorption of the substance by the tissues of the arterial region, as it was Braier's observation (1960-1961).

The toxic threshold for the arterial route in relation to the venous one, varied with the injected substance, since its absorption must be different for each drug, according to its affinity to the surrounding tissues. This fact shows that identical results cannot be generalized or induced to other substances: an experimental verification for each drug is necessary in order to define the difference between the venous and the arterial toxic dose for each one of them. Only then, the arterial injection of high doses of the most suitable substances for this purpose should be tried.

With this verification, new possibilities for chemotherapy can be foreseen, since it will eventually be possible to inject cytotoxic drugs intra-arterially and regionally

TABLE 1 — GUINEA-PIGS INJECTED INTRAVENOUSLY IN THE DISTAL CAVA VEIN AND INTRAARTERIALLY IN THE ABDOMINAL AORTA. 30 MINUTES OBSERVATION

Route of injection	Benzene in ml/kg of body weight							
	0,05	0,1	0,2	0,4	0,8	1,6	3,2	6,4
Venous	S S S S	S + + +	+ + + +	+ +	+ +	+ +	+ +	+ +
Arterial	S S	S S	S S	S S	S S	S S S S	S + + +	+ + + +

	Potassium cyanide mg/kg of body weight			
	5	10	20	40
Venous	S S S S	+ + + +	+ +	+ +
Arterial	S S	S S S S	+ + + +	+ +

	Snake venom (*Bothrops jararaca*) mg/kg of body weight — 60 minutes observation					
	0,25	0,5	1,0	2,0	4,0	8,0
Venous	S S S S	S S S +	+ + + +	+ +	+ +	+ +
Arterial	S S	S S S S	S S S S	S S S +	+ + + +	+ +

Each animal: S = survival + = death

TABLE 2 — DOGS INJECTED INTRAVENOUSLY IN THE FEMORAL VEIN AND INTRAARTERIALLY IN THE FEMORAL ARTERY. WITHOUT ANESTHESIA OR SKIN INCISION. 24 HOURS OBSERVATION

	Benzene in ml/kg of body weigth					
Route of injection	0,1	0,2	0,4	0,8	1,6	3,2
Venous	S S	S +(5) +(4) +(3)	+(2) +(2) +(8)	+(1) +(1) +(1)	+(2) +(1)	+(1) +(1)
Arterial	S S	S S S +(80)	+(120) +(240)	+(60) +(280)	+(60) +(6)	+(10) +(2)

Each animal: S = survival + = death, numbers indicate time of death in minutes.

in much higher doses than those utilized now, that would be lethal if injected intravenously. This way, the attainment of sterilizing or total chemotherapy could be possible for cases of localized tumours.

Summary

Anesthetized and laparotomized guinea-pigs were injected intravenously in the distal cava and intra-arterially in the abdominal aorta with several toxic substances. The observation time was 30 minutes for those injected with benzene and potassium cyanide and 60 minutes for those injected with snake venom.

There is a great difference between mortal doses, when a toxic substance is injected intra-arterially or intra-venously. The mortal dose was always greater by intra-arterial injection, and also distinct for each substance. For benzene, it was 0,2 ml/kg intravenously and 6,4 ml/kg intra-arterially. For potassium cyanide, it was 10 mg/kg intravenously and 20 mg/kg intra-arterially, and for snake venom (*Bothrops jararaca*), it was 1 mg/kg intravenously and 4 mg/kg intra-arterially.

Dogs not anesthetized or traumatized by surgery, showed twice more resistance to benzene injected in the femoral artery than in the femoral vein.

Resumo

Cobaias anestesiadas e laparotomizadas foram injetadas por via venosa na cava distal e por via arterial na aorta abdominal com várias substâncias tóxicas. O tempo de observação foi de 30 minutos para as injetadas com benzeno e cianureto de potássio, e de 60 minutos para as injetadas com veneno ofídico.

A dose mortal de benzeno foi de 0,2 ml/kg por via venosa e de 6,4 ml/kg por via arterial. A dose mortal de cianureto de potássio foi de 10 mg/kg por via venosa e 20 mg/kg por via arterial. O veneno de *Bothrops jararaca* foi mortal nas doses de 1 mg/kg por via venosa e 4 mg/kg por via arterial.

Cães não anestesiados nem traumatizados cirùrgicamente, injetados na veia ou na artéria femoral com benzeno, mostraram resistência duas vêzes maior quando injetados por via arterial.

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