Цена 12 к.

ACADEMY OF SCIENCES OF THE USSR
SCIENTIFIC CENTER OF BIOLOGICAL RESEARCH
INSTITUTE OF BIOLOGICAL PHYSICS

INFORMATION

FTOROSAN — OXYGEN CARRYING PERFLUOROCHEMICAL PLASMA SUBSTITUTE

PUSHCHINO • 1983

СОСТАВ И ХАРАКТЕРИСТИКА ФТОРОСАНА

1. Перфтордекалин (ПФД)	15,2 г
2. Перфторпараметилциклогексилперидин (ПМЦП)	7,6 г
3. Проксанол – оксиэтилированный полипропиленгликоль (M.W. 8000)	3,8 г
4. Хлорид натрия	0,6 г
5. Хлорид калия	0,04 г
6. Хлорид магния	0,02 г
7. Бикарбонат натрия	0,15 г
8. Хлорид кальция	0,03 г
9. D-глюкоза	0,18 г
10. Высокомолекулярный плазмо-экспандер (альбумин или оксиэтил-крахмал)	3,0 г
11. Вода для инъекций	до 100 мл

Содержание ионов фтора	$<3 \cdot 10^{-5}$ М
pH	7,4
Относительная вязкость	<3,5 сП
Осмотичность	360 мосм/л
Средний диаметр частиц эмульсии	0,1 мкм

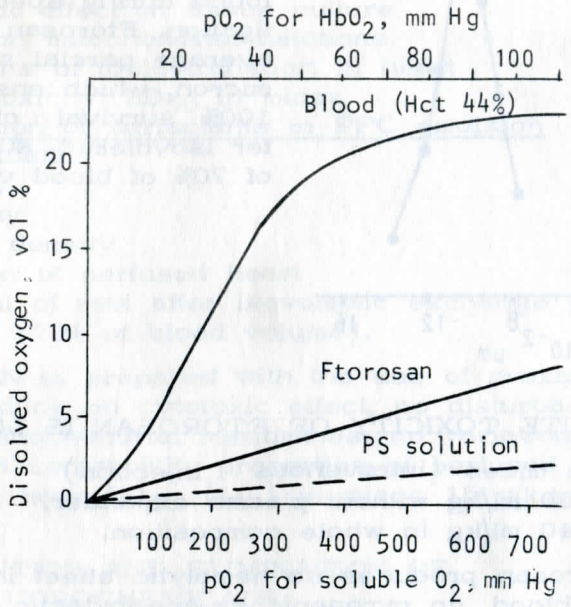
КИСЛОРОДТРАНСПОРТНУЮ ФУНКЦИЮ ВО ФТОРОСАНЕ ВЫПОЛНЯЮТ ЭМУЛЬГИРОВАННЫЕ ПЕРФТОРУГЛЕРОДЫ

Растворимость кислорода в растворе глюкозы, цельной крови и перфторуглеродах (pO_2 760 мм, T 25°C)

Глюкоза 5%	2,4 об %
Кровь (Htc. 45%)	22,0 об %
ПФД	42,0 об %
ПМЦП	40,0 об %

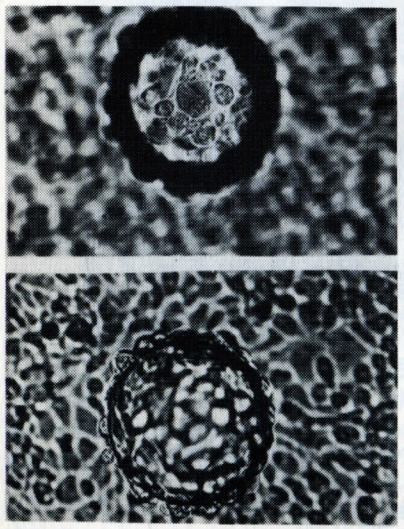
Кислородная емкость Фторосана в 3 раза больше, чем у любого плазмозаменителя.

Oxygen dissociation curves of Ftorosan, whole blood and Protein-salt solution (PSS).



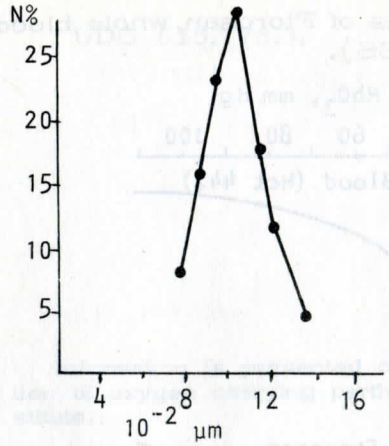
T O X I C I T Y

Obtaining nontoxic product is the main goal during preparation of Ftorosan. This can be done with physico-chemical and biological testing system.



PERFLUOROCHEMICALS, the basic components of Ftorosan, are chemically and metabolically inert, do not inhibit the growth of human lymphoid cells in tissue culture system, produce no aberrations in metaphase human lymphoid cells.

The growth of fibroblasts on the surface of PFC globule. In the upper micrograph the surface of globule is brought into focus, in the lower micrograph – the equator.

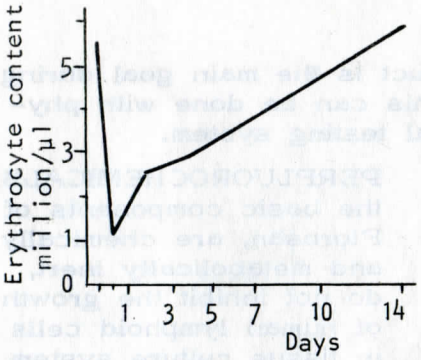


The optimal partical size distribution of Ftorosan was found during special investigation. Ftorosan has an average parcial size of 0.1 micron, which ensures a 100% survival of rats after isovolemic substitution of 70% of blood volume.

ACUTE TOXICITY OF FTOROSAN IS LOW

LD_{50} in mices (intravenous injection)
200 ml/kg without plasma expander,
140 ml/kg in whole composition.

Ftorosan produces no hemolytic effect in rat and human blood, no pyrogenic or anaphylactic reactions and does not inhibit hemopoesis.



Chronological changes of red blood cells in rats after exchange transfusion by Ftorosan (final Hb 4 g/dl).

THE KEY STEP OF FTOROSAN PREPARATION IS EVOLUATION OF SURFACTANTS

Testing protocol for emulsifying agents.

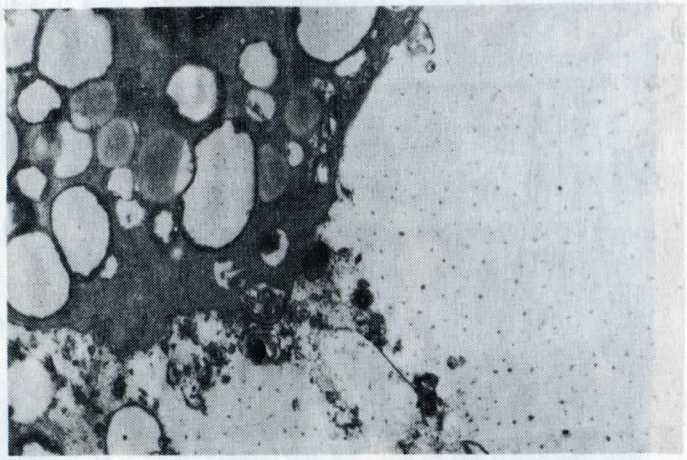
1. Physico-chemical methods
   - Infrared spectroscopy
   - Microcalorimetry
   - Estimation of molecular weight distribution
   - Measurement of interfacial tension
   - Determination of impurities

2. Biological testing
   - Interaction with biological molecules
   - Cytotoxic effect on tissue culture
   - Effect on mitochondrial functions
   - Variations of ionic transport in heart
   - Acute toxicity: LD_{50} in mices
3. Evoluation of surfactants in PFC emulsion
   - Emulsification
   - Stability
   - Viscosity
   - Optical density
   - Function of perfused heart
   - Survival of rats after isovolemic exchange perfusion (70% of blood volume).

FTOROSAN is prepared with the use of proxanols which produce no cytotoxic effect, no disturbances in cell and mitochondrial membranes, no variations in electrical and contractility properties of perfused heart, and which have LD_{50} (i.v.) in mices 15 g/kg.

RETENTION AND ELIMINATION OF PERFLUOROCHEMICALS

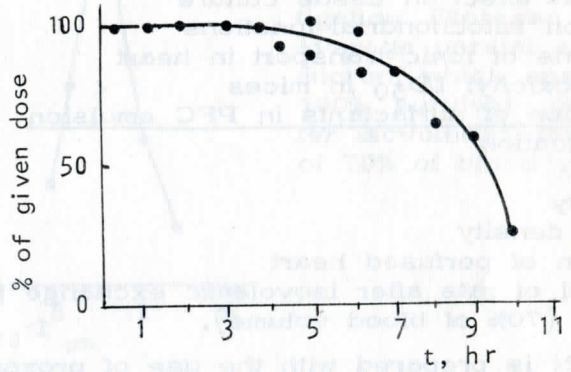
About 95% of PFCs are eliminated through lungs and skin, 2-7% of PFCs are excreted with bile.



Electron-micrograph of moving of PFC drops into alveolar duct (50000 x magnification). 5 days after intravenous injection of Ftorosan.

65-70% of the given PFCs are eliminated during 4-5 days.

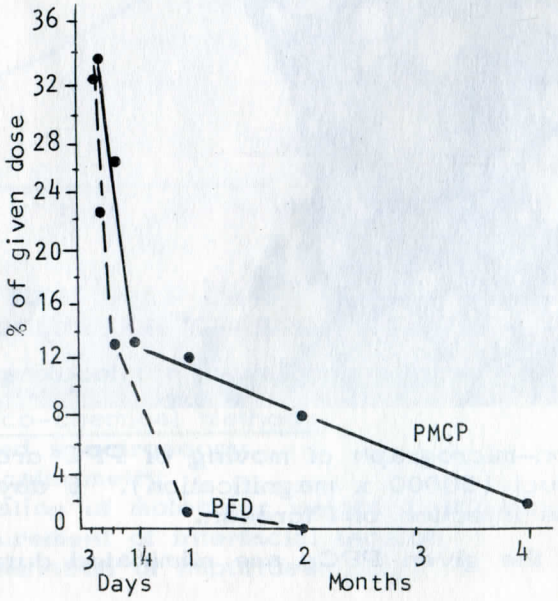
Blood retention of Ftorosan in rats after substitution of 70% of blood volume



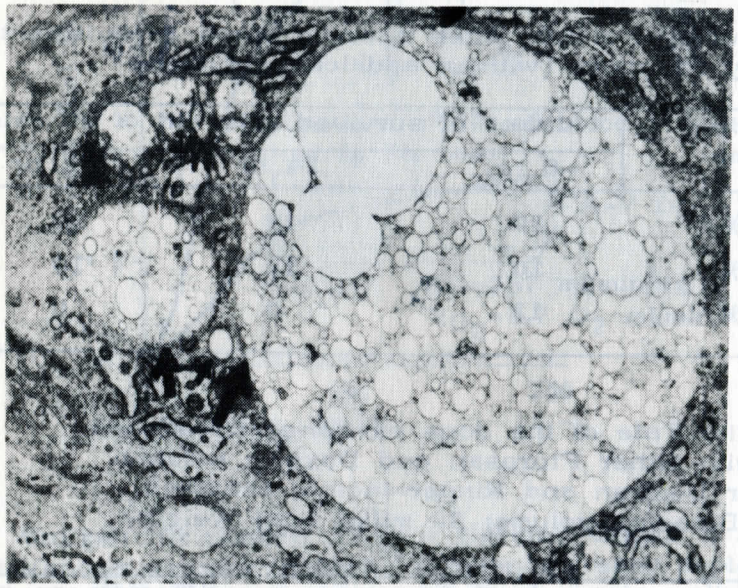
About 35% of the given PFCs are accumulated by

Liver	20-25%
Spleen	5-9%
Bone marrow	1-2%
Lungs	0.1-1%
Lymphatic tissue	0.1-1%

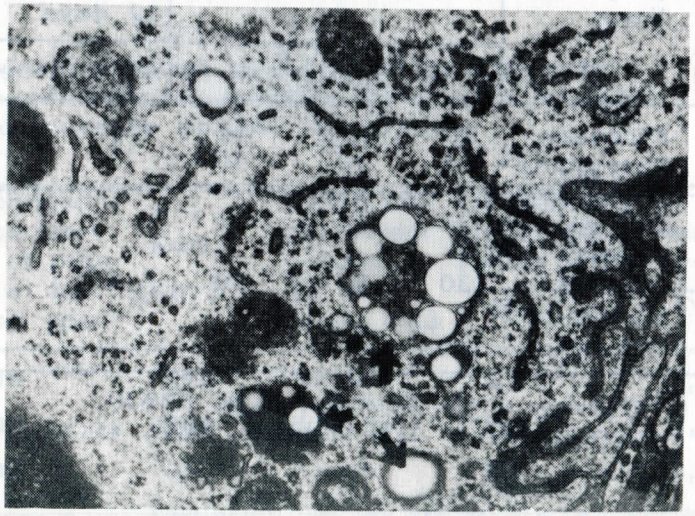
Retention of PFCs in rat organs after exchange transfusion of Ftorosan (dose: 12 g of PFCs /kg body weight).



Electron-micrograph of Kupffer's cells after exchange transfusion of Ftorosan



1 week after infusion



3 months after infusion

No histological damages are found in the tissues after elimination of PFCs.

SOME RESULTS ON MASSIVE BLOOD SUBSTITUTION BY FTOROSAN

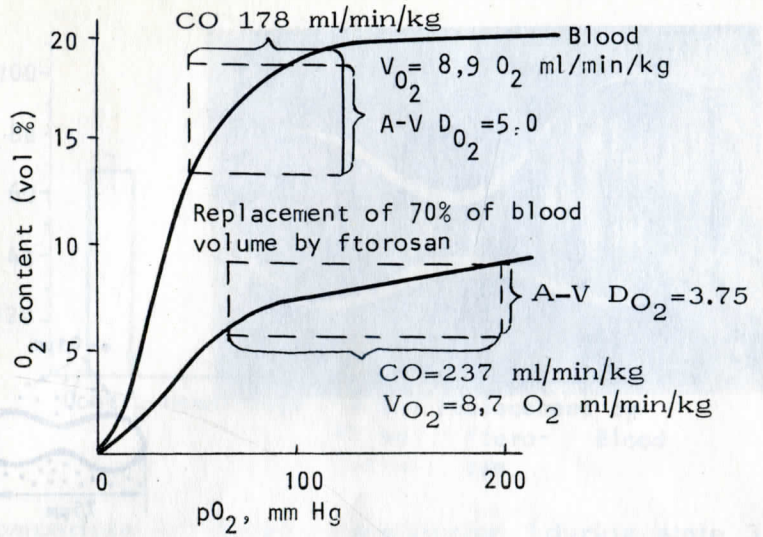
Survival of rats after massive blood replacement by Ftorosan (without additional infusions)

Bleeding volume	Number of survived rats out of 20 rats		
	8 hr	24 hr	72 hr
70%	19	19	19
85%	16	12	10
99%	12	0	0

The Fate of the dogs exchange-transfused with either Ftorosan and Dextran solution or Dextran and Ringer-lactate solutions (Bleeding volume: 50 ml/kg body weight)

Hemoglobin concentration (g/dl)	Type of preparations	Infusion volume (ml/kg body w.)			Results on partial blood replacement during 12 days	
		1 hr	24 hr	48 hr	alive	dead
3.8	Ftorosan	50	30	30	11	2
	Polyglucin*	30	30	30		
4.0	Polyglucin*	30	30	30	6	3
	Reopolyglucin**	30	30	30		
	Ringer-lactate sol.	30	–	–		

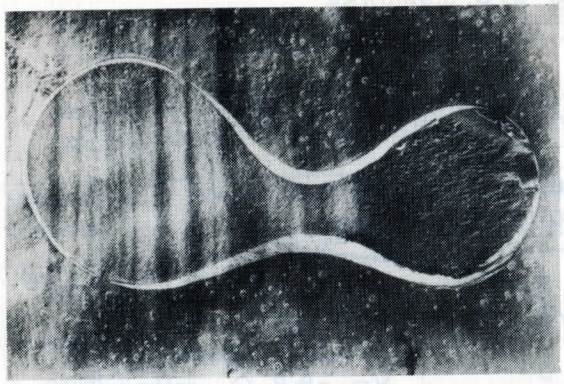
* Polyglucin – 6% Dextran, M.W. 60000.
** Reopolyglucin – 10% Dextran, M.W. 40000.

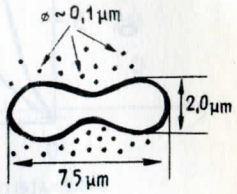


Oxygen consumtion (V_{O_2} = Cardiac Output x Arteral-Venous oxygen content difference) after replacement of 70% of blood volume of Ftorosan is maitained at normal level upon increasing cardiac output (CO) and arterial oxygen tension.

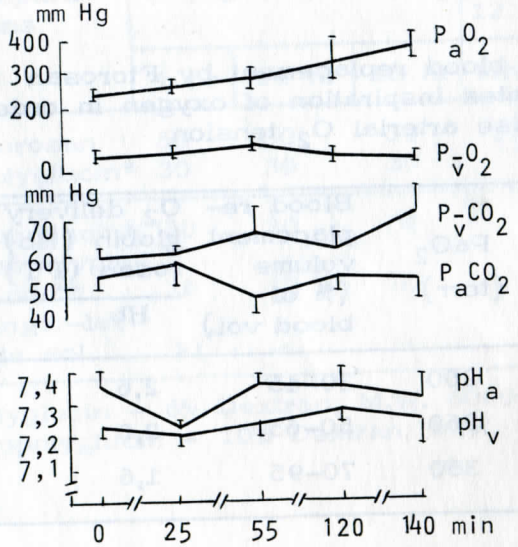
Massive blood replacement by Ftorosan necessitates inspiration of oxygen in order to increase arterial O_2 tension

Fractional concentration of oxygen in inspired gas	PaO_2 (torr)	Blood replacement volume (% of blood vol.)	O_2 delivery by Hemoglobin (Hb) and Ftorosan (FT) (vol %)	
			Hb	FT
40%	200	30–45	2,6	1,3
60%	260	50–65	2,0	2,0
100%	350	70–95	1,6	2,5

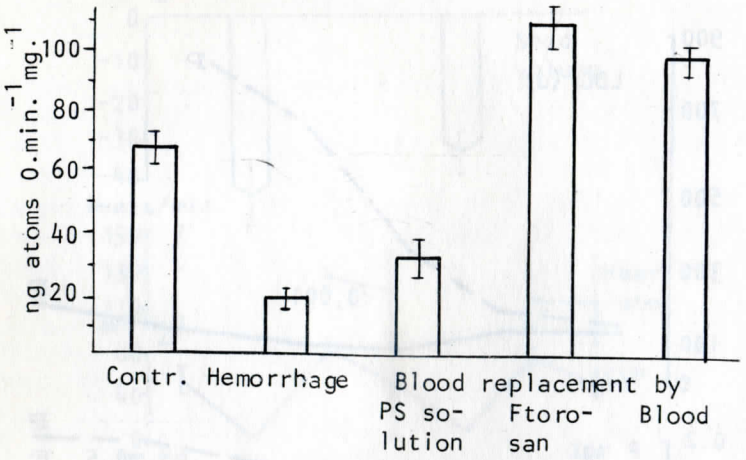




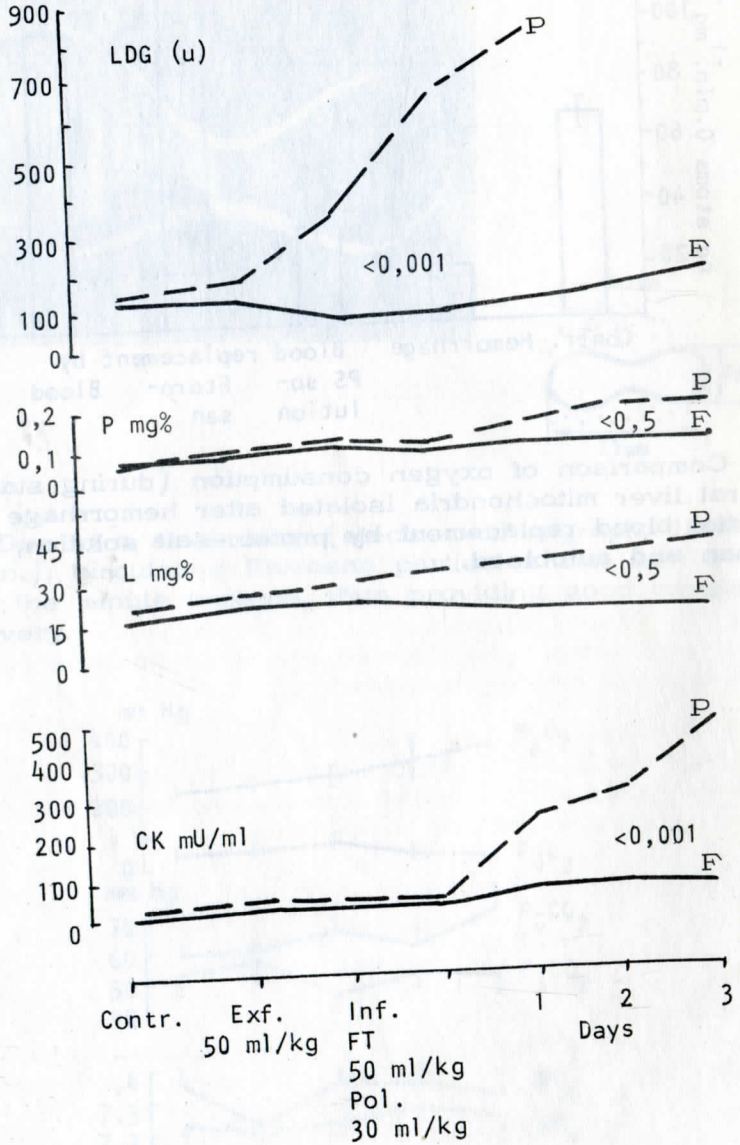
Due to a small size (electron-micrograph, 10000x magn.), circulating Ftorosan particales can flow through the minute vessels, thus providing good oxygen delivery.



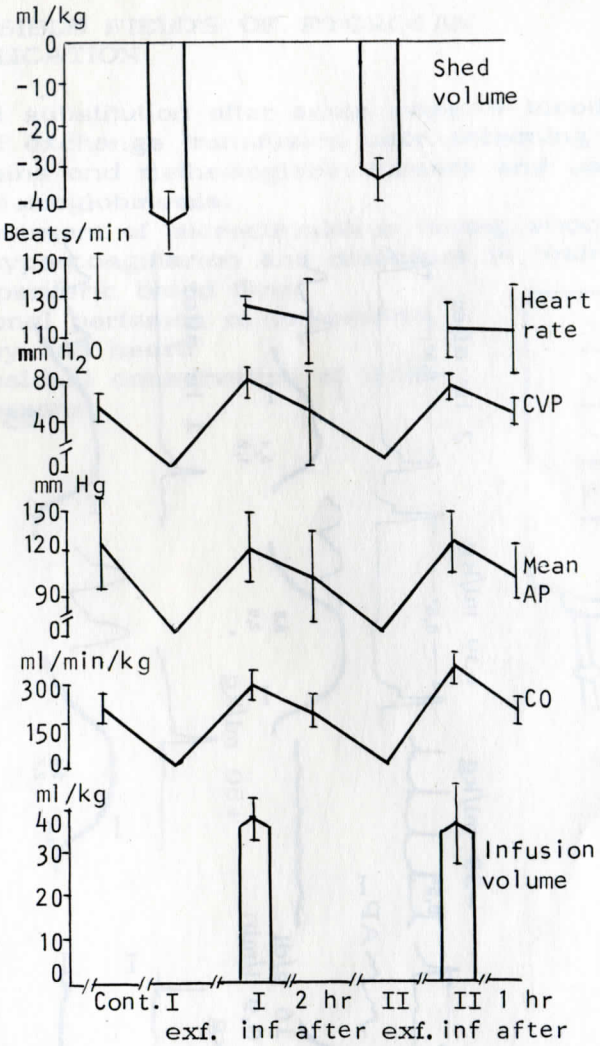
Blood oxygen and carbon dioxide tensions, blood pH after replacement of 70% of blood volume in rats by Ftorosan (inspired gas pO_2 500-600 torr).



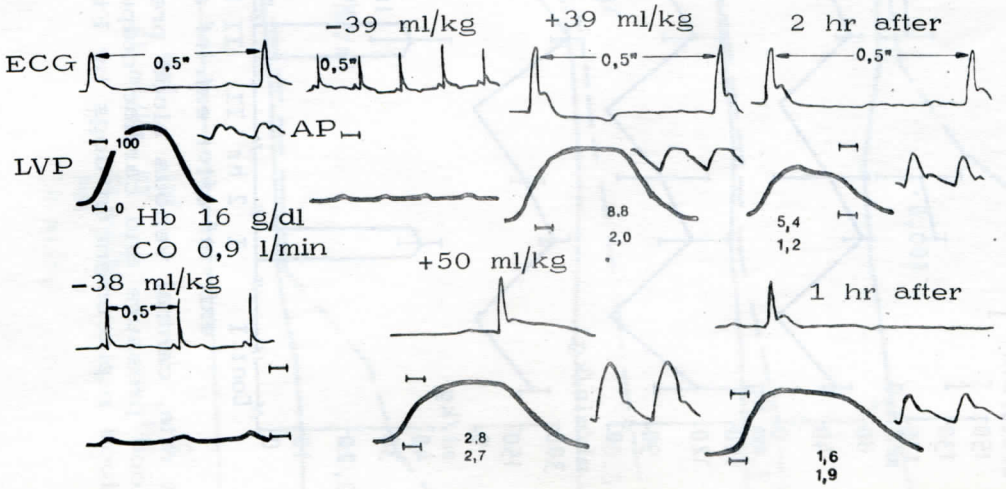
Comparison of oxygen consumption (during state 3) of rat liver mitochondria isolated after hemorrhage and partial blood replacement by protein-salt solution, Ftorosan and autoblood.



Activity of lactate dehydrogenase (LDG) and creatine kinase (CK), contents of pyruvate (P) and lactate (L) in dog blood are closer to normal value after partial blood replacement by Ftorosan, than by Polyglucin.



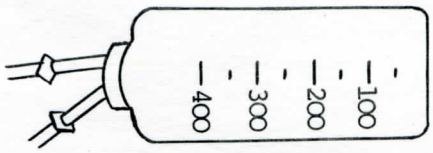
Heart rate, central venous blood pressure, mean aortic blood pressure and cardiac output after two-step partial blood replacement in dogs by Ftorosan.



Changes of ECG, aortic blood pressure (AP), left ventricular pressure (LVP) and cardiac output (CO) during two-step partial blood replacement in dogs by Ftorosan.

POSSIBLE FIELDS OF FTOROSAN APPLICATION

1. Blood substitution after acute massive blood losses.
2. Blood exchange transfusion upon poisoning by hemolysins and methemoglobin formers and upon carboxyhemoglobinemia.
3. Improvement of microcirculation during shock, stroke, hypercoagularion and disorders in brain, heart and periferic blood flow.
4. Regional perfusion of extremities, kidney and heart.
5. Perfusional conservation of isolated organs.



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