Isotonic Solutions XII

Permeability of Red Corpuscles to Various Water-Soluble Organic Iodine Compounds

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In the present investigation, inquiry was made into the penetration effects of certain water-soluble organic iodine compounds with respect to the human erythrocyte membrane. Employing the hemolytic method, van't Hoff factors were calculated for each compound. The results indicated that all compounds studied yielded hemolytic *i* values which were higher than *i* values obtained by the freezing point method. Experiments were also conducted in the presence of 0.2% sodium chloride; in some cases this had the effect of lowering the hemolytic *i* values. Some tests were made in which the defibrinated blood used in determination of hemolytic *i* values was replaced by whole blood containing heparin sodium. The *i* values obtained with heparinized blood were in agreement with the *i* values resulting from the use of defibrinated blood. None of the compounds studied appeared to cause hemolysis of erythrocytes by penetration of the cell; hemolysis was noted only in hypotonic solutions of these compounds.

PREVIOUS investigations (1–10) have dealt with the permeability of erythrocytes to a variety of chemical compounds. The purpose of the present study was to determine the permeability of erythrocytes to various water-soluble organic iodine compounds used as contrast media in roentgenographic diagnostic procedures. This class of compounds is administered parenterally in relatively high concentrations. No references were found in the literature on the permeability of erythrocytes to any of the compounds used in the present study. Hence, experiments were conducted to determine the hemolytic *i* values of some of the water-soluble organic iodine compounds; *i* values were also determined by the freezing point method.

EXPERIMENTAL

Collection of Blood.—In experiments utilizing defibrinated blood, samples were obtained and treated in precisely the same manner as described by Husa and co-workers (1–10). In experiments requiring heparinized blood, the sample was obtained in an identical fashion and immediately added to a 10-ml. graduated centrifuge tube which contained 0.05 ml. of heparin sodium solution, 10,000 units per ml., such that the 10-ml. heparinized blood sample contained 50 units of heparin sodium per ml. The centrifuge tube was inverted several times to insure thorough mixing, and the heparinized sample was then transferred to a 50-ml. Erlenmeyer flask and treated in the same manner as defibrinated blood.

Samples were obtained principally from the forearm veins of a 27-year old white male. On several occasions samples were generously donated by volunteers.

Preparation of Solutions.—Solutions of compounds which were available as water-soluble salts were prepared in essentially the same manner as described by other workers (1–10). Iodipamide sodium, iodipamide methylglucamine, and diatrizoate methylglucamine solutions were prepared by dissolving a quantity of the free acid in a solution containing an equimolar quantity of the proper base.

Calculation of Hemolytic *i* Values.—Quantitative determinations of per cent hemolysis and calculations of hemolytic *i* values were carried out in the manner described by Grosicki and Husa (2).

Chemicals.—All organic iodine compounds used in the investigation were generously contributed by their manufacturers: sodium diprotrizoate, sodium acetrizoate, and sodium iodohippurate by Mallinckrodt Chemical Works; sodium methiodal, iodopyracet, and sodium diatrizoate by Sterling-Winthrop Research Institute; iodipamide, diatrizoic acid, and methylglucamine by Squibb Institute for Chemical Research.

Freezing Point Determinations.—The apparatus used to determine the freezing points was that of Bartley (11), as modified by Husa and Adams (1). van't Hoff *i* factors were calculated according to the formula

$$\Delta T_f = K_f i m$$

where ΔT_f is the change in the freezing point of water after the addition of solute, K_f is the molal freezing point constant for water (1.86), i is the van't Hoff factor, and m is the molality of the solution.

Results with Heparinized Blood.—Some investigators (12) have used heparinized blood in experiments on isotonicity of solutions. Hence, the question arose as to whether results obtained with heparinized blood would be comparable with those using defibrinated blood. To throw light on this question, hemolytic *i* values were determined for the 10 compounds listed in Table I using the same procedure as before except that defibrinated blood was replaced by whole blood containing 50 units/ml. of heparin sodium. The *i* values obtained with

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TABLE I.—VALUES OF *i* FOR VARIOUS ORGANIC IODINE COMPOUNDS, CALCULATED FROM CONCENTRATIONS CAUSING 25, 50, AND 75 PER CENT HEMOLYSIS OF HUMAN ERYTHROCYTES[a]

Name of Compound	Hemolysis, % 25	50	75	Averages
Sodium diprotrizoate	2.34	2.40	2.54	2.43
Sodium diprotrizoate[b]	2.42	2.51	2.62	2.52
Sodium methiodal	1.93	1.94	1.98	1.95
Sodium methiodal[b]	1.99	2.03	2.07	2.03
Sodium acetrizoate	2.25	2.34	2.50	2.36
Sodium acetrizoate[b]	2.19	2.22	2.32	2.24
Sodium iodohippurate	2.15	2.19	2.27	2.20
Sodium iodohippurate[b]	2.15	2.17	2.23	2.18
Sodium iodomethamate	3.62	3.72	3.97	3.77
Sodium iodomethamate[b]	3.45	3.49	3.58	3.51
Iodipamide sodium	4.06	4.35	4.70	4.37
Iodipamide sodium[b]	3.73	3.84	3.94	3.84
Iodipamide methylglucamine	3.78	4.46	4.84	4.36
Iodipamide methylglucamine[b]	2.96	3.03	3.20	3.06
Iodopyracet	2.01	2.12	2.41	2.18
Iodopyracet[b]	1.61	1.61	1.64	1.63
Sodium diatrizoate	2.25	2.32	2.51	2.36
Sodium diatrizoate[b]	2.09	2.13	2.16	2.13
Diatrizoate methylglucamine	2.37	2.49	2.73	2.53
Diatrizoate methylglucamine[b]	2.48	2.54	2.75	2.59

[a] All *i* values represent an average of two blood samples.
[b] Values determined in the presence of 0.2% sodium chloride.

TABLE II.—VALUES OF *i* OF VARIOUS ORGANIC IODINE COMPOUNDS CALCULATED FROM FREEZING POINT DATA OBTAINED WITH A MODIFIED BARTLEY APPARATUS

Compound	Molality of Solution	Average Freezing Point Depression	*i* Value
Sodium diprotrizoate	0.025	0.087	1.87
Sodium methiodal	0.025	0.085	1.83
Sodium acetrizoate	0.025	0.089	1.91
Sodium iodohippurate	0.025	0.091	1.95
Sodium iodomethamate	0.025	0.138	2.97
Iodipamide sodium	0.025	0.138	2.97
Iodipamide methylglucamine	0.025	0.137	2.94
Iodopyracet	0.025	0.077	1.66
Sodium diatrizoate	0.025	0.091	1.95
Diatrizoate methylglucamine	0.025	0.093	2.00

heparinized blood agreed closely with the *i* values which resulted from the use of defibrinated blood, the differences being within experimental error.

DISCUSSION

The values of *i* obtained by the hemolytic method for the organic iodine compounds were consistently higher than the corresponding *i* values obtained by the freezing point method (see Table II). In solutions of some substances, erythrocytes lose electrolytes from within the cell, thus causing a decrease in internal osmotic pressure and a corresponding ncrease in resistance to hemolysis (2). Possibly such exosmosis from erythrocytes may occur in solutions of the organic iodine compounds, causing the higher *i* values obtained experimentally.

The difference between the hemolytic *i* value and the *i* value obtained by the freezing point method was smallest with sodium methiodal; in this case the hemolytic *i* value was 1.95 and the *i* value by the freezing point method was 1.83. In this connection it is of interest to note that sodium methiodal was the only nonaromatic compound used in this investigation.

The exosmosis from erythrocytes in solutions of some substances can be corrected in some cases by addition of a small proportion of sodium chloride (2). The presence of 0.2% sodium chloride reduced the hemolytic *i* values of some of the compounds tested, *e.g.*, sodium iodomethamate, iodipamide sodium, and iodipamide methylglucamine. In case of iodopyracet the hemolytic *i* value was reduced from 2.18 to 1.63 by the presence of 0.2% sodium chloride; the latter value agreed closely with the *i* value of 1.66 obtained by the freezing point method. For some of the other compounds, the abnormally high values of *i* by the hemolytic method were not reduced by the presence of 0.2% sodium chloride.

SUMMARY

1. Hemolytic *i* values obtained for various organic iodine compounds were consistently higher than the corresponding *i* values obtained by the freezing point method. In some, but not all, cases the hemolytic *i* values were lowered by the presence of 0.2% sodium chloride.

2. The organic iodine compounds tested apparently do not penetrate the human erythrocyte.

3. Hemolytic *i* values obtained for the organic iodine compounds using defibrinated blood were in agreement with similar values obtained with heparinized blood.

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