A Study of the Potential Interaction of Valsartan with some Electrolytes

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Abstract

The effect of electrolytes (salts) on the partition coefficient of valsartan was studied at room temperature. The investigation was done by partitioning valsartan between 1-octanol and electrolyte solutions of varying concentrations. It was found that all the electrolytes increased the partition coefficient of the drug except sodium fluoride. The effect was found to depend on the size and charge of the ions present in solution.

Keywords: Potential interaction, *Valsartan,* Monovalent electrolytes, Divalent electrolytes

Introduction

Valsartan, N-[p-(o-1H-tetrazol-5-ylphenyl) benzyl]-N-valeryl-L-valine is a potent, long-acting non-peptide AII type 1 receptor antagonist (Latif *et al.,* 2001). It is used clinically in the treatment of hypertension. Valsartan has very limited aqueous solubility, thus its pharmacokinetics depends largely on its solubility in the lipoidal membrane of the body. The aim of the study was to investigate potential interaction between the drug and antacids, dietary supplements or caloric agents and replacement preparations. These pharmaceutical dosage forms often contain one or more electrolytes. The knowledge gained from the investigation could provide better understanding in the management of patients (particularly geriatric patients) on valsartan and pharmaceutical preparations containing electrolytes. Previous reports have shown correlation between absorption, distribution and partition coefficient (Martin *et al.,* 1973); pharmacological activity and partition coefficient (Hansch and Dunn, 1972; Bawden *et al.,* 1983). In other reports (Gadalla *et al.,* 1974; Mbah 2008), partition coefficient of medicinal agents has been observed to be influenced by electrolytes. It is against this background, that we studied the potential interaction between valsartan and electrolytes by partitioning the drug between 1-octanol and electrolyte solutions.

Materials and Methods

Materials: Valsartan (Norvartis Pharmaceuticals, USA), benzoic acid (Fisher Scientific, USA), barium chloride, lithium chloride, calcium chloride, magnesium chloride, sodium bromide, sodium chloride, sodium fluoride, sodium sulfate, potassium chloride and potassium iodide and 1-octanol (Sigma-Aldrich, USA).

Apparatus and HPLC conditions: All separations were done with Hitachi LC6200 pump and AS2000 autosampler, Kratos spectroflow 783 detector. A zorbax analytical column C_{18}, 150 mm x 4.6 mm, 3.5 µm was used.

High performance liquid chromatographic procedure: The mobile phase consisted of 1 % aqueous acetic acid in methanol. The flow rate was 1 ml/min at room temperature. The injection volume was 10 µl and the detection was effected at 254 nm.

Standard solution: Stock solution of valsartan (94 µg/ml) and internal standard (400 µg/ml) were prepared in methanol. Aliquots (9.40-46.9 µg/ml) of the standard stock solution were pipetted into a 10 ml flask. A 1ml aliquot of the internal standard (benzoic acid) was added to each flask and diluted to volume with methanol.

Partition coefficient measurement: Partition coefficient was determined in 1-octanol-water systems. Aqueous solutions of different molar concentrations of electrolytes were prepared each containing 24 mg of valsartan in 20 ml. To the aqueous phase was added 20 ml of 1-octanol. The flasks were stoppered and agitated at room temperature for 2 h to achieve complete equilibration. The aqueous phase was analysed by HPLC method for valsartan content and its concentration was calculated from preconstructed calibration curve. The partition coefficient of valsartan was calculated from equation 1 (Johansen and Bungaard, 1980a) thus: P = CoVw / CwVo = (C ı - Cw) Vw / (Cw) Vo ---------- eq. 1, where P = partition coefficient; Co = concentration of valsartan in the organic phase; C ı = initial concentration of valsartan in the aqueous phase; Cw = concentration of valsartan in the aqueous phase; Vw = volume in the aqueous phase; Vo = volume of the organic phase.

Results and Discussion

The calibration graph of valsartan was linear in the range of 9.40-46.9 µg/ml. Peak area ratio versus concentration relationship is described by regression equation A = 0.0133 + 0.0775C (r = 0.9999). The effects of electrolytes on the partition coefficient of valsartan are presented in Tables 1 and 2. The results in table 1 indicated that all the monovalent electrolytes increase the partition coefficient of valsartan except sodium fluoride. The increase in partition coefficient was observed to increase as the concentration of the electrolyte is increased except for potassium iodide where the effect was found to be independent of molar concentration. It was found that with some salts, the effect was higher, the higher the molecular weight of the monovalent cation.

Table 1: Effect of monovalent electrolytes on the partitioning of valsartan between distilled water and 1-octanol

Electrolyte concentration	Partition coefficient of valsartan					
(mol/L)	LiCl	NaF	NaCl	NaBr	KCl	KI
0.00	22.2	22.2	22.2	22.2	22.2	22.2
0.05	46.0	14.0	30.3	32.5	32.7	36.7
0.10	54.7	9.80	36.2	37.9	38.2	36.1
0.20	83.4	6.30	42.6	44.2	45.3	35.8
0.40	114.2	4.10	56.0	61.7	62.5	34.4
1.00	218.5	2.50	79.2	145.3	109.8	33.9

Table 2: Effect of divalent electrolytes on the partitioning of valsartan between distilled water and 1-octanol

Electrolyte concentration	Partition coefficient of valsartan			
(mol/L)	Na SO_4	$MgCl_2$	$CaCl_2$	$BaCl_2$
0.00	22.2	22.2	22.2	22.2
0.05	35.9	43.4	44.1	39.5
0.10	43.5	53.4	54.7	44.7
0.20	50.2	66.0	83.5	69.6
0.40	72.9	101.5	138.0	91.3
1.00	219.2	207.1	258.7	147.5

For instance, at a molar concentration of NaCl, the partition coefficient is 79.2 while that obtained for the drug in the same concentration of KCl is 109.8. The same observation was noted for monovalent anion. For example, at a molar concentration of NaF the partition coefficient of valsartan is 2.5 while molar concentrations of NaCl and NaBr showed partition coefficients of to be 79.2 and 145.3 respectively. The results in Table 2 indicated that divalent electrolytes increase the partition coefficient of valsartan. This effect was observed to increase as the concentration of the divalent salts is increased. With some electrolytes, the increase in the partition coefficient of valsartan was higher the higher the molecular weight of the cation or anion and the charges on the ions. For instance, the partition coefficient of valsartan in a molar concentration of $MgCl_2$ was 207.1 while that obtained for the drug at the same concentration of $CaCl_2$ was 258.7. Also sodium sulfate when compared to other sodium salts gave the greatest increase in the partition coefficient of the drug. This could be as a result of the charge size of the sulfate ion and its dehydrating effect. The effect of the electrolytes on the partition coefficient of valsartan could be explained by dehydrating effect, salting-in and salting-out effects. For instance, the observation that the partition coefficient of the drug in a molar concentration of LiCl was 218.5, higher than NaCl 79.2 suggests that lithium chloride has greater salting-out effect than sodium chloride. This could be explained by assuming more hydration of the lithium ion than sodium ion thereby reducing the density of aqueous environment around valsartan molecules with a resultant decrease in aqueous solubility of the drug. The significant decreased effect on the partition coefficient of valsartan by sodium fluoride could probably be explained by salting-in effect. This involved the ionization of valsartan due to the alkaline pH of the solution; the increased aqueous environment around the drug and the stabilization of valsartan ions by the sodium fluoride ions with the resultant increase in the drug aqueous solubility.

Conclusion: All the electrolytes studied increased the partition coefficient of valsartan, except sodium fluoride. The increasing effect was observed with increasing electrolyte concentration except with potassium iodide. Based on the previous study (Mbah 2005), pH control could also have an effect on the partition coefficient of the drug. Finally, the investigation suggests that potential interaction exist between valsartan and pharmaceutical preparations containing electrolytes and such interaction could give rise to altered pharmacological effect. This could be of benefit to patients who concomitantly take valsartan and ion-removing agents but not replacement preparations.

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