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Osmotic agents in continuous ambulatory peritoneal dialysis

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OSMOTIC AGENTS IN CAPD

SUMMARY

It is well established that the peritoneum is not an "ideal" semipermeable membrane, but a partially one. Glucose, wich is the only osmotic agent in common use for peritoneal dialysis, readily permeates through it, leading to a rapid exponential decline in the ultrafiltration rate.

It is clear that an optimal osmotic agent is one providing sustained ultrafiltration with minimal absorption.

Among small molecular weight agents with limited human experiences and success are glycerol and amino acids.

On the other hand, attempts to emulate the phenomenon of colloid osmosis with large molecular weight agents, have not been succesful. Glucose polymers (MW 20000) have been effective to get ultrafiltration up to 12 hours with lower calorie loads than glucose solutions. Perhaps a combination of low and high molecular weight substances (eg. glucose + glucose polymer, or amino acids + glucose polymer) with synergiatic effects of their different ultrafiltration profiles may be appropiate.

As yet there is no available agent to replace glucose.

AGENTES OSMOTICOS EN DPCA

RESUMEN

Ha sido bien establecido que el peritoneo no es una membrana semipermeable ideal, sino parcialmente semipermeable. La glucosa, único agente osmótico en uso actual para diálisis peritoneal, le atraviesa fácilmente, con el consiguiente declinar rápido de su capacidad de inducir ultrafiltración.

El agente osmótico óptimo es aquel que, proporcionando máxima ultrafiltración, tenga mínima absorción peritoneal.

Entre los agentes de pequeño peso molecular con experiencias y éxitos limitados están el glicerol y los aminoácidos. Entre los de gran peso molecular ninguno resultó con éxito. Intermedios son los polímeros de glucosa (PM 20000), que se han mostrado efectivos en mantener ultrafiltración por encima de las doce horas con menor aporte calórico que las soluciones con glucosa.

Quizás una combinación de varios tipos de sustancias (por ejemplo, glucosa + polímero de glucosa o aminoácidos + polímero de glucosa) con efectos sinergísticos de sus modos de acción y perfiles de ultrafiltración sean los más apropiados para el futuro. De momento no disponemos de ningún agente para sustituir a la glucosa.

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Introduction

Osmosis is a phenomenon of paramount significance for transport of water to solutes through biological and artificial membranes of widely differing composition. This principal is therapeutically utilised in the practice of peritoneal dialysis.

The early concept of osmosis as applied to peritoneal dialysis was based on the principal that a solution instilled into the peritoneal cavity, made relatively hypertonic to plasma, would lead to ultrafiltration, whilst hypotonic or isotonic saline solutions led to fluid reabsorption, this was noted as long ago as 1876 [1, 2]. This confirmed the belief that the magnitude of ultrafiltration was directly related to the osmolality gradient. Since small molecular weight solutes generate greater osmolality per unit mass, these agents (crystalloids) were regarded as the most effective osmotic agents. Of the number of small molecular weight agents evaluated in animals [3], only glucose appeared to be safe as well as effective and readily metabolised.

In the 1960's, the use of intermittent peritoneal dialysis (IPD) in the management of patients with end-stage renal failure confirmed the long term safety of glucose [4]. Although a rapid decline in osmotic gradient, as a consequence of glucose absorption, was already recognised, it was of little significance during short dwell $^{30\text{-}60}$ IPD. In 1976. The concept of long dwell (4-10 h) dialysis (CAPD), however highlighted the short duration of effective ultrafiltration (2-3 h) associated with use of glucose [5]. If ultrafiltration of greater magnitude or duration was required, this deficiency was partly overcome by further increasing the osmolality and the concentration of glucose. This shortcoming of glucose in CAPD prompted a closer look at the factors which influence the magnitude and direction of osmotic forces.

Factors influencing osmotic forces

In clinical practice it is customary to sample the two fluids that are seperated by a membrane and determine their osmolalities, which is a measure of total number of solute particles in a solution. The osmotic flow is then assumed to be in accordance with the magnitude of the osmotic gradient. Whilst this relationship holds true for an ideal semi-permeable membrane (one that is permeable to water only), for a membrane that is partially permeable to solutes, as most biological membranes are, this concept is not strictly valid. Since only impermeant solutes exert an osmotic force, the osmotic flow across such a membrane is determined by the concentration gradient of impermeable solutes rather than the difference in the total number of solutes across it (i.e. osmolality). In order to characterise the precise relationship between solutes and the membrane, Staverman introduced the concept of the reflection coefficient ( ) whose value ranged from zero (for solute as permeable as water) to unity (for one that is totally impermeable) [6]. Hence, the magnitude and direction of the osmotic forces across membrane is determined by the differences of the sum of the products of the reflection coefficients and molar concentration of solutes [7]. It follows, therefore, that whilst no net flow occurs between isosmotic solutions seperated by an "ideal" semipermeable membrane, it may do if seperated by a permeable membrane, provided an appropiate choice is made of solutes with different reflection coefficients. Thus, with a permeable membrane, the magnitude and the direction of the osmotic force is significantly influenced by the physico-chemical characteristics of the solute (molecular size, shape deformability and charge). This phenomenon is the basis of "colloid" osmotic flow induced by albumin across the capillary wall.

GLUCOSE AS AN OSMOTIC AGENT IN CAPD

It is well established that the peritoneum is not an "ideal" semipermeable membrane, but a partially permeable one. Glucose, which is the only osmotic agent in common use, readily permeates through it, leading to a rapid exponential decline in the ultrafiltration rate with time ultrafiltration eventually ceases at 2-3 hours and reabsorption begins (Negative UF).

Other disadvantages are: a) the continuous daily absorption of 150-300 grams of glucose from the dialysate leading to hyperinsulinaemia, hyperlipidaemia and obesity [9], b) the low pH of this solution may alter host difence [10], c) the high osmolality of the solutions with possible damage to the peritoneum [11], d) glucose breakdown products especially with storage and possible loss of UF [12].

Other osmotic agents for CAPD

Whilst there is no readily available ideal osmotic agent for long dwell dialysis, it is clear that an optimal agent is one providing sustained ultrafiltration with minimal absorption. Albumin (MW 68,000 daltons), impermeable to the capillary wall, is the most effective osmotic agent encountered in biological systems but it is prohibitively expensive to be considered a substitute for glucose.

Small molecular weight agents

One line of research has concentrated on minimising

the metabolic effects of glucose rather than ultrafiltration deficiencies by studying agents with molecular size similar to or smaller than glucose (Table I). These have differed from glucose by their ability to utilise alternative metabolic pathways, thereby offering potential advantages such as reduce insulin stimulation and calorie load. In the majority of cases the rate of transperitoneal absorption exceeds the metabolic capacity resulting in serious hyperosmolar syndromes [14-17]. Amongs these, two agents have had some limited human experiences and success.

Table I

Agents	MWT	Charge	Disadvantages	Ref
Glucose	182	NIL	See text.	8
Fructose	182	NIL	Similar to glucose, hyperosmolality.	14
Xylitol	152	NIL	Lactic acidosis, hyperosmolality.	15
Sorbitol	122	NIL	Hyperosmolality.	16
Glycerol	92	NIL	Short UF, hyperosmolality limited to diabetics.	17-21
Amino acids	75-214	±	No optimal formular elevated urea levels, acidosis, high costs.	22-24
Low molecular weights				
Large molecular weight				
Polyanions	90,000-500,000	−ve	Toxic to peritoneum cardiovascular instability (rats).	17, 25
Polycations	40,000-60,000	+ve		
Neutral Dextran	60,000-35,000	NIL	Low UF, absorption metabolism?	26
Gelatin	20,000-35,000	±	Allergenic, viscous accumulation/metabolism?	17, 25
Glucose	20,000-22,000	NIL	Accumulation of maltose.	26-27
Ideal osmotic agent				
Albumin	68,000	−ve	Prohibitively expensive.	13

Glycerol: Being a smaller molecule than glucose and therefore with higher osmolality per unit mass, it produces greater ultrafiltration than glucose but of shorter duration [18]. Long term use of glycerol has been limited to managing patients with diabetes mellitus, but exacerbation of hypertriglyceridaemia remains a problem [20, 21]. There appear to be no overt advantage over glucose to its more widespread use.

Amino acids: Solutions of amino acids appear to be an attractive alternative to glucose. Based on animal studies, Oreopoulos et al. [22] suggested that amino acids may safely be used as osmotic agents. Subsequently the same group showed that the ultrafiltration patterns of 1 % and 2 % amino acids solutions were similar to those of 2.5 % and 4.25 % glucose solutions, respectively [23]. The use of 1 % amino acids solution alternated with glucose in six patients over a period of 4 weeks was well tolerated and led to improved nutritional status without systemic or local side effects [24]. However, there are several problems associated with its use: the optimal ratio of essential to non-essential amino acids in the dialysate is yet to determined; rising urea levels as well as acidosis and its high manufacturing costs. The long term effectiveness is also unknown and needs further study.

Large molecular weight agents

The other pathway of research has been to alter the ultrafiltration profile as well as minimising the metabolic disadvantage of glucose by using large molecular weight agents. These would be less readily absorbed, giving rises to sustained ultrafiltration with reduced calorie load. The problem with the use of these substances is related to the need to have a much greater mass to achieve the equivalent osmolality gradient of a small molecular weight substance. At high concentrations these molecules are less soluble, hyperviscous, non-phyaiological and can be allergenic [16]. However, one may question the need to have a very high molar concentration of these substances to produce sufficent osmotic forces for ultrafiltration. The phenomenon of "colloid" osmosis, as highlighted by albumin, could be utilised in peritoneal dialysis. This would have the advantage of achieving substained ultrafiltration at low molar concentration using dialysis solutions isosmotic to plasma.

Early attempts to emulate this phenomenon using charged and neutral macromolecules (Table I) have not been successful.

Glucose polymers

Isolated by fractionation of hydrolysed corn starch, these are a mixture of oligo-polysaccharides of variable chain length, ranging from 4 to > 300 glucose units linked predominantly by 1-4 linkages. Using 5 %

isosmotic solution of glucose polymer (MW 20,000) we have shown sustained ultrafiltration up to 12 hours and substantially lower calorie load per ml of ultrafiltrate than glucose solutions [27]. In addition a hyposmolar solution of glucose polymer was able to achieve sustained ultrafiltrate over a 12 hour period [28]. The major problem with its use, which as yet lacks any long term experience, is the accumulation of the final breakdown product of glucose polymer, maltose (disaccharide). This obviously needs further study.

FUTURE TRENDS IN OSMOTIC AGENTS FOR CAPD

For short dwell peritoneal dialysis, low molecular weight osmotic agents are most effective and glucose is probably the best and safest agent. However, for long dwell processes like CAPD, the aims should be to achieve a more physiological isosmotic solution, capable of producing sustained ultrafiltration. Perhaps a combination of low and high molecular weight substances (eg glucose + glucose polymer; or amino acids + glucose polymer) with synergistic effects of their different ultrafiltration profiles may be appropiate; the low molecular weight substance giving early ultrafiltration which is sustained by the action of large molecular weight agent. The exact proportion of these combinations would be determined by the duration of the exchanges required.

As yet there is no readily available agent to replace glucose. Promising substances are amino acids and glucose polymers, both of which need further extensive study.

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