EFFECT OF DEXTRAN 40 ON URINE FLOW

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SOON after the introduction of dextran 40 (low-molecular-weight dextran; Rheomacrodex; Lomodex), a dextran fraction with an average molecular weight of 40,000, it was noted that its infusion induced an increase in urine flow both in normal men (Gelin, Persson and Zederfeldt, 1961) and in postoperative patients (Gelin, 1961). It is perhaps understandable that these observations, made against a background of confidence in the significance of the biorheological properties of dextran 40, should have been taken as evidence of a beneficial effect on renal function. They may also have encouraged the use of dextran 40 in acute renal failure, both experimentally (Atik, Manale and Pearson, 1962; 1963) and clinically (Bergentz, Gelin, Rudenstam and Zederfeldt, 1961).

There are a number of ways in which dextran 40 may improve blood flow and recent high resolution studies of the microcirculation confirm that definite improvement occurs (Engeset, Stalker and Matheson, 1966a). In addition, these studies show that plasma volume expansion and haemodilution are important factors in this improvement. But the rheological property peculiar to dextran 40 is claimed to be its effect in preventing or reversing erythrocyte aggregation (Gelin and Ingelman, 1961). Despite earlier uncertainty (Matheson, 1964) that stemmed from the indirect nature of much of the evidence taken to support this disaggregating property, a recent "blind" controlled study has shown that dextran 40 has a disaggregating effect on human erythrocytes that cannot be attributed to dilution and is superior to that of other dextran fractions (Engeset, Stalker and Matheson, 1966b). However, the relationship between erythrocyte disaggregation and a diuretic effect need not be causal. It is known that dextran fractions of higher molecular weight also induce an increase in urine flow (Wallenius, 1950; Bergström, Bucht, Ek, Josephson and Werkö, 1959) and further, the renal physiologic and pathologic implications of intravascular erythrocyte aggregation are unknown. Precise dissection of the effects of dextran 40

on urine flow and composition is clearly a matter of physiologic interest and, in addition, must provide basic information that should properly precede interpretation of effects as beneficial.

Experiments in which osmolal clearance and solute-free water excretion were calculated after infusion of dextran 40 in mildly hydropenic normal men showed that, although the diuresis is in part determined by the crystalloid (dextrose or sodium chloride) present in the infusate, the particular effect of dextran 40 is to augment the excretion of free water (Matheson, Irvin and Hedley, 1964). To explain this effect it is pertinent to consider three possible mechanisms.

After dextran 40 infusion the smaller molecules are rapidly excreted and large quantities of dextran appear in the urine. High urine dextran concentrations have little effect on total osmolality but render the urine hyperoncotic. It may be questioned whether the oncotic gradient established in favour of the tubular urine might limit water re-absorption. The nature of the diuresis is compatible with such a theory since the urine, despite high dextran concentrations, remains more or less dilute in terms of total solute. Thus, water retained in the tubular urine by reason of a colloid osmotic effect would appear to be solute free. However, there are arguments against the hypothetical mechanism of "colloid osmotic diuresis". First, it has been shown that in the perfused tubules of *Necturus*, the addition of protein to the luminal fluid does not impede the re-absorption of water, although it does abolish or reverse the colloid osmotic gradient (Whittembury, Oken, Windhager and Solomon, 1959). Secondly, complete inhibition of the diuretic effect of dextran 40 with physiological doses of vasopressin, despite the excretion of remarkably hyperoncotic urine, (Matheson and others, 1964) shows that in man, as in *Necturus*, the creation of an apparently steep oncotic gradient between the tubular urine and the tubule cells has little effect on the tubular handling of water. These findings indicate that another mechanism must underlie

the diuretic effect of dextran 40 and emphasise that evidence in favour of the use of osmotic diuretics such as mannitol in incipient acute renal failure is inapplicable to dextran 40.

Presumably the most pertinent consideration is whether the effect of dextran 40 on free water excretion could be the result of changes in renal haemodynamics. It is generally accepted that renal medullary hypertonicity is maintained by countercurrent multiplication and it is likely that a passive process of countercurrent diffusion in the vasa recta minimises the rate of dissipation of the medullary osmotic gradient (Gottschalk, Lassiter, Mylle, Ullrich, Schmidt-Nielsen, O'Dell and Pehling, 1963). Since the efficiency of a countercurrent system varies inversely with the velocity of flow within it, alteration in the rate of vasa recta perfusion might influence the concentrating process, and in theory, if sodium transport continued unaltered in the presence of relative medullary hypotonicity, medullary hyperaemia could promote increased free water excretion. In addition, there are reasons to suppose that infusion of dextran 40 may augment medullary perfusion. First, medullary blood flow appears to vary independently of total renal blood flow (Kramer, Thureau and Deetjen, 1960) and, in contrast to the situation in the cortex, may not be subject to auto-regulation (Thureau and Deetjen, 1962). Secondly, according to the cell-separation theory (Pappenheimer and Kinter, 1956) at constant total renal blood flow any dilutional effect of dextran 40 on blood viscosity is likely to result in increased flow of cell-poor plasma through the medulla. Thirdly it has recently been shown that infusion of dextran 40 in man is followed by a significant increase in effective renal plasma flow (Matheson, 1966) which makes the conclusion in favour of medullary hyperperfusion even more compelling. Inhibition of the diuresis by vasopressin does not necessarily exclude medullary hyperaemia as a possible mechanism since present concepts of the action of anti-diuretic hormone (ADH) are largely inferential: its precise role in the maintenance or re-establishment of maximal medullary hypertonicity is unknown.

The possible role of "volume receptors" in the diuresis after dextran 40 should also be considered. Previously, evidence that pressure changes within the vascular compartment can affect the release of ADH lacked conviction (O'Connor, 1962) but recent experiments, in which improved techniques for the measurement of ADH in blood were used, give direct support to this hypothesis (Weinstein, Berne

and Sachs, 1960; Share, 1961). Thus, diminished ADH secretion in response to plasma volume expansion affords a convenient explanation for the water diuresis that follows infusion of dextran 40. The characteristics of the response and its inhibition with vasopressin are compatible with this explanation. Alternative mechanisms have been considered (Matheson, 1965) but are less likely than either medullary hyperperfusion or diminished ADH release.

Experiments in dogs show that if venous blood is withdrawn apace with the dextran infusion so that the central venous pressure remains normal, effects on free water excretion are abolished (Matheson, 1965). Thus, the hypothesis that these effects result from plasma volume expansion is strengthened. Further, dilutional effects on medullary perfusion must be augmented by venesection and, although haemodynamic changes in response to volume expansion cannot be completely excluded, the hypothetical role of improved medullary perfusion in the diuretic mechanism of dextran 40 is rendered more speculative. The evidence is in favour of the conclusion that diminished ADH secretion in response to plasma volume expansion underlies the increase in free water excretion.

Thus, it is illogical to attach therapeutic significance to dextran 40 induced diuresis and suggestions that the diuresis may be beneficial after operation are even less meaningful since the characteristic effect of dextran 40 is then prevented by postoperative antidiuresis (Matheson, Harper, Hedley and Irvin, 1965). A small and variable osmotic diuresis follows the infusion of dextran 40 after operation and is accounted for by the crystalloid contained in the infusate (Matheson and others, 1965).

Although the findings described give no support to the theory that dextran 40 may benefit renal function they should not be taken as evidence against such a possibility. It may be questioned whether the increase in renal plasma flow that follows infusion of dextran 40 after operation (Matheson, 1966), together with alterations in intrarenal haemodynamics, does not imply a beneficial effect whatever the changes in the composition of the urine. Such a possibility is admitted, but it may be noted that, since dextran fractions of higher molecular weight induce at least equal increments in renal plasma flow (Matheson, 1966), these changes, like those in urine flow, are most likely the result of plasma volume expansion. Thus, if any benefit to renal function accrues from the use of dextran 40, either this benefit results from

plasma volume expansion, or erythrocyte aggregation is a hitherto unrecognised cause of impaired function. Further, since effects on renal perfusion can be beneficial only in situations where perfusion is abnormal, it is most pertinent to consider possible effects in acute renal failure.

The results of evaluation of the effects of dextran 40 in simulated acute renal failure in animals are conflicting (Atik and others, 1962; 1963; Shumacker, Hawtof, Herendeen, Judd and Webb, 1964) and clinical experience with dextran 40 has led to the suspicion that its administration, instead of preventing the condition, may even be an aetiological factor.

Six patients who developed acute oliguric renal failure in association with the administration of dextran 40 have been described (Gracey, 1965; Wilkinson, 1966; Daniel, Mohamed and Matheson, 1966). Disquiet also arises from the histological finding of "osmotic nephrosis", characterised by tubular dilation with swelling and vacuolation of the tubule cells, at autopsy in patients who had been given dextran 40 (Dahlgren, 1963; Wilkinson, 1966). But, in the six patients mentioned there was, in general, adequate cause for anuria without incriminating dextran. In addition, although there is little doubt that the histological changes described result from the presence of dextran in the tubular urine and in the tubule cells, they are also found when the urine contains other solutes, such as glucose and mannitol, in quantity and are usually held to be functional rather than pathological. There is no certainty that tubular dilatation and cellular swelling aggravates renal ischaemia or accelerates the course of tubular necrosis. In addition, short-term studies show no impairment of maximal tubular excretory capacity (Matheson, 1965).

However, there is another theoretical hazard of dextran 40: after its infusion in antidiuretic subjects, the urine, because of its high dextran content, becomes very viscous. It has been suggested (Gelin, personal communication, 1965) that despite tubular dilatation, which is a physiologic prerequisite to the transport of this viscid fluid, distal tubular obstruction may thereby occur. During experiments on anti-diuretic patients after operation we have never observed a reduction in urine flow since the crystalloid component of the infusate invariably induced a small osmotic effect. (Matheson and others, 1965). But, it may be reasoned that if tubular damage were already established such an effect could no longer operate. Under these

circumstances it seems possible, especially if the capacity of the tubules to dilate were limited, that a large increase in urine viscosity could aggravate oliguria even to the extent of causing anuria. Further, Wickham and Sharma (1965) have recently put forward reasons for thinking that the rate of urine flow may be an important factor in acute renal failure. Thus, although the available evidence is certainly inadequate to incriminate dextran 40 as an aetiological factor it seems reasonable to speculate that it may adversely affect the course of established acute renal failure. Therefore, since in any event there is at present no evidence that erythrocyte aggregation plays a part in acute renal failure, or that changes in renal function consequent on plasma volume expansion are therapeutically important, it seems wise to discourage the use of dextran 40 in this condition. Further, until more information from studies of the relationship between urine viscosity and urine flow rate in hyponatremia and other circumstances is available, suspicion of impending renal failure should indicate the need for caution in the use of dextran 40 in patients who might otherwise benefit from it.

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