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EDITORIAL

Just how benign is renal dopamine?

For more than 15 years intravenous (i.v.) infusions of low dose dopamine have been widely used for their renoprotective effect, both in the critically ill and those at risk of renal dysfunction undergoing major surgery. Although the practice is still widespread there is little evidence to support this role [1] and furthermore, recent reviews have argued against routine 'renal dopamine' [2,3]. Whilst the evidence in favour of dopamine is weak, its use has been justified by the potentially grave prognosis of patients who develop acute renal failure (ARF) [4,5].

Dopamine was initially used in the belief that clinical research would follow to confirm that it is renoprotective. A consistent feature of the published trials is that low dose dopamine infusions increase urine output [6]. The trials differ on whether they attribute this to a systemic inotropic effect [7] or to local actions in the kidney such as arterial vasodilatation and inhibition of renal tubular sodium reabsorption [8]. However, studies have been unable to demonstrate that dopamine can prevent ARF or reduce mortality [9]. The rationale for its use has therefore changed to, 'it may not prevent renal failue but fluid balance is easier to manage in non-oliguric patients and at least it's harmless'.

This benign label for dopamine is in spite of the fact that low doses may cause haemodynamic effects such as tachyarrhythmias, increased cardiac preload and afterload, myocardial ischaemia and exacerbation of hypovolaemia. Conventional teaching is that low doses (0.5–2.5 μg kg^{-1} min^{-1}) of dopamine have a specific dopaminergic effect, and only at higher doses do the β (3–5 μg kg^{-1} min^{-1}) and α (>5 μg kg^{-1} min^{-1}) adrenergic responses occur. However, in practice, inter-patient variation and altered drug handling in acute illness [10] make the haemodynamic response to low dose dopamine unpredictable [11]. From a respiratory point of view, dopamine has been shown to reduce hypoxic respiratory drive [12] and increase intrapulmonary shunt [13].

There are four other areas that have not been widely considered and must question whether renal dopamine is truly benign. The first is oliguria. This is preferable to a dopamine-induced diuresis if the problem is actually hypovolaemia – a condition which cannot always be excluded even with a pulmonary artery catheter. Whilst patients in intensive care with renal impairment continue to pass some urine there may also be a reluctance to start haemofiltration. Although not without its own complications, haemofiltration corrects metabolic derangements and allows better feeding regimes. In addition, oliguria can be because of tubuloglomerular feedback (TGF), the process by which the kidney lowers the glomerular filtration rate to protect itself from ischaemic damage [14]. Ischaemia is a major aetiological cause of ARF even though the kidneys receive up to 25% of cardiac output. The renal medulla is the most vulnerable region because the counter current exchange mechanism and 'portal' nature of its blood supply normally render it in a state of borderline hypoxia. If the medullary tubular cells become ischaemic they fail to reabsorb sodium which is an energy dependent process. Consequently, excess sodium chloride reaches the distal tubule and by the process of TGF glomerular filtration is reduced. In turn this decreases the filtrate reaching the tubules thereby reducing the metabolic work and oxygen consumption of the medulla. Dopamine decreases oxygen consumption in the renal tubules by its diuretic action blocking solute reabsorption but it also antagonises TGF with the risk of causing ischaemia [15]. The overall effect of dopamine on medullary oxygenation probably depends on the patient's circulating volume status and cardiac output.

Second, concern has recently been raised about the possible adverse effects of dopamine on the splanchnic circulation. It was thought that dopamine and its synthetic analogue dopexamine not only selectively improved renal blood flow but also increased splanchnic perfusion in critically ill patients, lessening the risk of ischaemia and subsequent reperfusion injury. This

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is highly controversial but some studies have cast doubt on whether dopaminergic agonists selectively increase splanchnic blood flow [16] or if this necessarily reduces gut mucosal ischaemia [17]. These studies illustrate the concept that increasing an organ's perfusion may not be beneficial if the blood flow is then shunted across critical tissue beds.

Third, recent work has shown that dopamine depresses anterior pituitary function except for ACTH secretion. Dopamine infusions of 5 μg kg^{-1} min^{-1} in multiple trauma patients suppressed prolactin, LH and growth hormone secretion [18,19]. Perhaps most interestingly, dopamine exacerbated the so called 'sick euthyroid syndrome of critical illness' [20] – namely low T_4 T_3 and TSH levels, with a raised rT_3. Whilst this could be beneficial because it decreases protein catabolism by reducing the metabolic rate, it must also obtund the body's acute endocrine response to stress. In addition, T_3 is one of the body's endogenous inotropes [21]. Earlier work in healthy subjects has already shown that low dose dopamine (0.5 μg kg^{-1} min^{-1}) significantly suppresses prolactin secretion [22].

Finally, dopamine may alter immunological function via its inhibitory effect on prolactin secretion. Hypophysectomy or inhibition of prolactin secretion causes humoral and cell mediated immunosuppression in rats that can be reversed with exogenous prolactin [23]. Indeed the dopamine analogue bromocriptine, by inducing hypoprolactinaemia, has been used in humans and animals as an immunosuppressant to reduce transplant rejection [24,25].

Prolactin receptors have been identified on T and B lymphocytes that not only respond to circulating prolactin but also to a prolactin-like substance produced locally by lymphocytes [26]. Lymphocyte proliferation has also been shown to be inhibited *in vitro* by anti prolactin sera [27] and by bromocriptine [28, 29] indicating that dopamine has immunosuppressive actions independent of the pituitary. A study in six intensive care patients by Devins *et al*. [30] is the only work so far to look at the effect of dopamine on immune function *in vivo*. It showed that dopamine infusions of 5 μg kg^{-1} min^{-1} or more produced a temporary but significant fall in blood lymphocyte count and in the T cell response to a mitogenic stimulus. As yet these experiments have not been repeated with lower doses of dopamine, but it is worrying that iatrogenic endocrine dysfunction and immunosuppression may be caused by a drug with no proved benefit on outcome.

Clearly, there is no simple panacea for renoprotection in the critically ill. However, with concerns growing about the adverse effects of dopamine, management of oliguria should concentrate on appropriate resuscitation and accurate assessment of fluid status – guided by at least the use of a pulmonary artery catheter. Properly controlled clinical trials are needed to determine whether dopamine can in fact alter the course of renal dysfunction and to evaluate its safety.

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