DRUGS AND RENAL TOXICITY

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ABSTRACT

Because of the severity of acute renal failure prognosis in the intensive care units, preventive measures must be applied when using of nephrotoxic agents. No magic bullet exists to prevent drugs from causing renal dysfunction. Therefore, harmful agents for renal function should be ordered only when significant benefit is expected for the patient. The control for associated risks factors for renal failure, the preservation of renal perfusion and appropriateness of order are simple measures that can be easily applied. The issues that three nephrotoxic agents (i.e. plasma expanders, aminoglycosides, contrast media) are frequently used in critically ill patients is the topic of this study.

Key words: *Renal toxicity; drug*

I. INTRODUCTION

The severity of the prognosis of acute renal failure ICU patients requires every effort in order to preserve renal function. No molecule has clearly demonstrated efficacy to prevent the occurrence of kidney damage after administration of a nephrotoxic medicament. However, simple measures such as preservation of renal perfusion, respect for rules limitation, and the choice of a drug class can minimize deleterious are possible. A considerable number of substancea has been implicated in the genesis acute renal failure. For daily practice resuscitation, three drug classes deserve to be addressed given their frequency of use and the possibility of preventive measures: products with iodinated contrast, aminoglycosides and plasma expanders.

II. DEFINITION OF NEPHROTOXICITY

There is no definition of nephrotoxicity, including the evaluation of a new molecule before being put on the market. In addition, many renal toxicity criteria were used. If the measurement or assessment of GFR are the most often employed methods, other more sensitive parameters such as dosage of proteins and/or enzymes or tubular urine examination by magnetic resonance have also been proposed. These techniques allow early detection of tubular lesions, even before the onset of degradation of the glomerular function. However they can not be used in daily practice and their results remain controversial. The criterion of judgment most often employed in the literature is an increase in creatinine of 44 µmol/l (0.5mg/dl). If the impact on the prognosis of such a minimal increase in serum creatinine is widely demonstrated in patients hospitalized in room, it remains for evaluation in our resuscitation of patients.

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III. KIDNEY DAMAGE MECHANISMS

The most common mechanism of toxicity is the necrosis acute tubular. However we must not ignore the other possible injuries because of some impose measures in the specific supported. An alteration of the infusion by renal vasodilation of the efferent arterioles and/or vasoconstriction of the afferent arterioles, interstitial nephritis immunoallergic, osmotic nephrosis lesions and thrombotic microangiopathy maybe a drug-induced.

IV. EPIDEMIOLOGY

In hospitalized patients, the frequency of acute kidney deficiencies related to the administration of a substance nephrotoxic seems to be constant over the last 20 years. This frequency is about 20%, but the comparison between studies is difficult because of the lack of consensual definition. Elderly patients are particularly exposed since the nephrotoxic is the first cause of acute kidney failure in patients over 65 years. However, the type of molecules involved is changing. If the anti-infections remain in the first position (25%) inhibitors converting enzyme are increasing and are at the second place (22%) as nephrotoxicity contrast agents appears to decrease. Patients resuscitation, acute renal insufficiency of toxic origin is declining, from 20 to 4% between the two french epidemiological studies from 1991 and 1997. This decrease is possibly related to a change in the type acute renal failure supported in services resuscitation.

V. NEPHROTOXICITY OF IODINATED CONTRAST AGENTS

The definition of nephropathy associated with iodinated contrast media is relatively constant in clinical studies. This is an increase of serum creatinine of 44 mmol/l within 48 hours after injection. The incidence varies from 1 to 24% by pre-existing risk factors, mainly renal function before injection.

Both preventive measures that have clearly demonstrated their efficacy in patients at risk are the hydration and the use of products of low osmolarity. Several hydration protocols have been proposed. Initially perfusing one liter of 4.5% saline surrounding the injection (12 hours before and 12 hours after dosing) was proposed. More recently, a study suggests that the administration of bicarbonate solution is more effective. Regarless the type of contrast medium used, be aware that despite the reduction in osmolarity, the risk of toxicity persists among the highest risk -patients with chronic renal failure are diabetics.

Because of the likely involvement of free radicals in the genesis of this nephropathy, the use of antioxidant molecules has been proposed. The simplest of them, oral N-acetyl cysteine (NAC) was compared to hydration in a large number of tests, either for achieving scanners or arteriography. The studies showing a significant reduction of renal dysfunction in patients treated 48 hours prior to injection NAC were published in major journals.

In most studies it is interesting to note that changes in serum creatinine after injection of iodinated contrast was stable in the placebo group and decreased in the NAC group as one could expect stability in the NAC group and increased in the placebo group. The decrease in plasma creatinine may be secondary to increased secretion of creatinine by the kidney tubules after administration of NAC. It should also be remembered that the toxic mechanism of iodinated contrast agents is not only related to oxidative phenomena but also vascular.

If it has been shown that even hemodialysis could eliminate iodinated contrast agents, it is ineffective or even dangerous for the prevention of kidney disease.

Finally, simple preventive measures such as stopping the associated drugs favoring the appearance of renal failure (ACE inhibitor, nonsteroidal anti-inflammatory, diuretic) should not be forgotten, which unfortunately too often followed properly.

VI. NEPHROTOXICITY OF AMINOGLYCOSIDES

The pathophysiology of renal aminoglycoside toxicity is complex and imperfectly known. Schematically, aminoglycosides are filtered unmetabolised and reabsorbed by the renal tubules. After fixation of phospholipid membrane receptors, they penetrate the tubular cells where they induce structural and functional changes (inhibition of phospholipases, release of free radicals, function abnormality mitochondrial ...) leading to cell death.

Previously, aminoside was used twice/day. Currently, in a number of clinical studies, with once/day, 30-50% of drug accumulation in renal cortex, there were less nephrotoxic than before. Morever, the drug concentration in the blood caused apeak of bactericidal antibiotic, they increase effectiveness in treatment. Patients with normal renal function are prescribed with a dose once /day 3 mg/kg of Gentamycin and Tobramycin, 4mg/ day for Neltimicin, 15mg /kg to Amikacin. With patients with renal impairment, the dose went according to creatinine clearance.

Table 1: Adaptation of the duration of administration interval according to the creatinine clearance

Duration of interval (h)	Clearance creatinine (ml/min)
24	> 60
36	40 - 59
48	20 -39
>48 (control serum)	< 20

VII. ACUTE RENAL FAILURE AND PLASMA EXPANDERS

A number of arguments in the literature suggest that the administration of a colloid may be responsible for impaired renal function. Two mechanisms may be mentioned. Firstly osmotic nephrosis type tubular lesions have been reported in patients treated with dextran or hydroxyethyl starch (HES).

Furthermore, infusion of colloid osmotic solution could alter hemodynamics intraglomerular. Indeed, glomerular filtration is determined by Starling's law with a filtration pressure represented by the difference between the hydrostatic pressure gradient and the oncotic pressure gradient across the glomerular capillary wall. The hydrostatic pressure inside the glomerular capillary is very low (about 60 mmHg) in a normal subject. However, due to significant fluid filtration, intracapillary oncotic pressure increases along the glomerular capillary. When the oncotic pressure gradient becomes equal to the hydrostatic pressure gradient, the filtration pressure is zero and the filtration ceases. In cases of chock, the hydrostatic pressure in glomerular capillaries raises sharply, in this condition, glomerular filtration pressure is dependent on pression oncotique plasmatique.

Several animal studies show that intracapillary modifications of the oncotic pressure can cause opposite changes in the glomerular filtration rate. Few clinical studies have focused on this. Several cases of acute renal failure associated with elevation of important secondary oncotic pressure colloid infusion have been reported. On healthy volunteers in whom hypovolemia simulation was performed by salt restriction, administration of albumin was accompanied by a decrease in the glomerular filtration rate despite a significant volume expansion. To inverse that, the use of a hypo-oncotic solution for priming an extracorporeal circulation was described as can improve kidney function.

The SAFE study (Saline vs Albumin Fluid Evaluation) comparing the use of albumin 4% that of a crystalloid on nearly 7000 patients admitted to intensive care only found no difference in renal prognosis.

The type of colloid used also seems to influence the risk of kidney failure. One case reported in the literature suggests the occurrence of acute renal failure after infusion of gelatin. Cases of impaired dextrans renal function after treatment are however

numerous. Deterioration of glomerular filtration rate after albumin infusion was found in burnt patients and patients with trauma.

VIII. CONCLUSION

The care of a critically ill patient is often choosing the best diagnostic attitude and/or therapeutic depending on the individual risk benefit ratio but it is also collective. This is particularly true for the problem of nephrotoxicity. The possibility of an alternative non or less toxic therapy should always be considered. Potential nephrotoxic agents should be used if they have a profit significant. Finally, before considering the use promising compounds for renal protection, uncertain about effectiveness, simple compliance prescription nephrotoxic drugs and correcting risk factors associated with renal insufficiency should be achieved.

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