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DRUG NEPHROTOXICITY

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INTRODUCTION

The very basis of pharmacology is that drug action, either beneficial or toxic, depends upon the concentration of drug in the region of the receptor or among the molecules with which it reacts (1). For any drug to exhibit toxicity selectively to a particular tissue the drug must either achieve a higher concentration within that tissue compared to all others and/or the tissue must have functional characteristics (either physiological or biochemical) that render it more sensitive to the drug. Only in exceptional circumstances does the rate of blood flow to a tissue have any influence on tissue toxicity (2). For example, the kidney, which has the highest rate of blood flow of all the organs in the body, will be exposed to a concentration identical to the rest of the body during the elimination phase of drug excretion (2). Higher concentrations will be achieved only in the relatively brief distributional phase of drug absorption and elimination.

Some of the factors that influence the drug concentration in the kidney are as follows. The kidney filters large volumes of fluid and small solutes, including drugs, across the endothelium of the glomerular capillaries into Bowman's space of the glomerulus and then into the lumen of the nephron. Multiple specific mechanisms for the transport of different drugs across the tubular epithelium of the nephron can modify the concentration of drugs. When the rate of water reabsorption exceeds the rate of drug reabsorption from the nephron, the concentration of the drug increases in the lumen. When the transport process itself delivers the drug either into the tubular fluid or into the tubular cell, the luminal concentration of the drug is either increased or decreased, and the cellular concentration is inversely affected (1). Thus, the tubular fluid drug concentration in the Bowman's space is equivalent to arterial nonprotein bound plasma concentration, and the final drug concentra-

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tion in tubular fluid is equivalent to the concentration in the voided urine (1), assuming that no change has been exhibited by the transitional epithelium at the ureter and bladder or by bacteria. Between these two extremes, the concentrations can vary by as much as three orders of magnitude, depending upon secretion and/or reabsorption of the drug, water reabsorption, effects of pH and the Kp (oil/water partition coefficient) (1). Additional factors include the binding of plasma protein, rate of urine flow, and presence of analogous compounds that might influence transport.

Nephrotoxic effects of drugs within tubular fluid can be mediated by a direct action on the luminal membrane or by influence on concentrations of the drug in the cell or interstitium due to reabsorption (1,2). Other physiological and biochemical characteristics that are uniquely combined in the kidney will, in some instances, render the organ more susceptible to toxic effects.

We have not embarked here upon a comprehensive review of all agents known to be nephrotoxic. Rather, we have selected those nephrotoxic agents that highlight one or several of the above-mentioned mechanisms, those for which there have been recent advances in the understanding of their toxicity, or those for which promising directions of research are possible.

AMINOGLYCOSIDES

Aminoglycosides all consist of two or more amino sugars joined in glycosidic linkage to a hexose nucleus, usually in a central position. They are polycations with a high degree of polarity and water solubility.

Nephrotoxicity related to aminoglycosides remains a major limitation in their clinical use. In a review of over 10,000 patients in 144 published clinical trials using aminoglycosides, Kahlmeter & Dahlager (3) reported average frequencies of nephrotoxicity resulting from gentamicin and tobramycin of 14% and 12.7%, respectively, and from netilmicin and amikicin, 8.7% and 9.4%, respectively. Localization studies have shown a selective accumulation of aminoglycosides in the renal cortex, mainly related to the pars convoluta (S1 and S2) portion of the proximal tubule (4). Autoradiographic studies demonstrate rapid proximal tubular uptake within endocytic vacuoles within 6 hr of administration of tritiated gentamicin (5).

At least 80% of renal accumulation of gentamicin occurs through filtration and tubular reabsorption. A smaller proportion may be absorbed from the basolateral membrane, but this is quantitatively less important in the cellular accumulation of aminoglycosides (6). Gentamicin uptake is of a low affinity/high capacity type and shows evidence of saturation kinetics. At low doses, tissue levels decline steadily, following first order kinetics. Aminoglycoside concentrations within the cortex will exceed by 2–5 times the plasma concentrations or concentrations in other tissues. The concentration achieved is

related to the aminoglycoside type and is directly correlated with the magnitude of toxicity, e.g. the toxicity of neomycin > gentamicin > tobramycin. At high doses a rapid decrease occurs in cortical concentration one to two days after the loading dose. This dissociation indicates a process of acute liberation of gentamicin from cells (or release from necrotic cells), and this correlates with morphological changes of tubular cell necrosis and regeneration (7).

Being cationic drugs, aminoglycosides bind to anionic phospholipids located on the tubular cell apical membrane, with the phosphoinositides acting as the principal receptor for aminoglycosides (8). The binding of the drug to receptor is followed by pinocytosis of the drug receptor complex, with subsequent translocation of the complex to a secondary lysosome (8). Within the lysosome the pH is more acidic than the cytoplasm, and this increases gentamicin binding to phospholipids. The binding of cationic aminoglycosides to negatively charged phospholipid bilayers impairs the degradation of phosphatidylinositol by binding to phosphatidylinositol 4,5 bisphosphate, thus preventing its metabolism and the release of inositol triphosphate (9, 10). The binding of aminoglycosides to cellular membranes also alters the activation and redistribution of the protein kinase C complex. The net effect is a generalized impairment of the phosphatidylinositol cascade, which may be an early initiating event in aminoglycoside nephrotoxicity (10).

The inhibition of phospholipid breakdown depends on the number of amino groups carried by the drug and the position of these groups, and on the chemical environment surrounding the drug molecule. Brasseur et al (11) demonstrated that the binding of aminoglycosides to phospholipids is related to the number of positively charged groups and the relative position of these groups in the aminoglycoside molecule. This modifies the insertion and degree of binding to the phospholipid layer, particularly in relationship to the ester bond split by phospholipases which is critical for the inhibition of phospholipid hydrolysis (11–13).

Aminoglycosides impair the metabolism and interconversion of phosphoinositides (14). This probably results in modification of calcium membrane transport processes and other membrane bound receptor functions that control cellular integrity. This may lead to cellular injuries and inhibition of repair to damaged membranes (8, 14). Calcium inhibits gentamicin-renal membrane binding, and calcium loading may protect against gentamicin-induced renal tubular cell injury (15). Gentamicin enhances the generation of hydrogen peroxide by mitochondria in vitro at levels of gentamicin comparable to those achieved in vivo (16). With the generation of hydrogen peroxide, other reactive oxygen metabolites, such as the superoxide anion and hydroxyl radicals, are readily formed. Hydroxyl radical scavengers and iron chelators have been shown to have a protective effect in gentamicin-induced acute

renal failure (17; P. D. Walker, personal communication), which implicates hydroxyl radicals in the generation of aminoglycoside nephrotoxicity. Hydroxyl radicals interact with numerous cellular processes and may cause membrane phospholipid peroxidation which is seen in aminoglycoside nephrotoxicity (8, 18). These reactions may not be the principal event: The use of antioxidants diphenyl-phenylenediamine and vitamin E prevented gentamicin induced lipid peroxidation but did not prevent the development of acute renal failure (18–20). This suggests that lipid peroxidation is a consequence of gentamicin toxicity and not a primary event in the development of cellular injury (19). However, the generation of hydroxyl radicals and their subsequent interaction with other biochemical events within the cell may be an initiating event in the development of cellular damage following aminoglycoside therapy. This hypothesis needs further testing.

Gentamicin inhibits oxidative phosphorylation in renal cortical mitochondria in vitro (21). This is probably mediated by alterations in membrane permeability due to alterations in mitochondrial calcium transport, which would then lead to alterations in mitochondrial respiration (21, 22).

Single nephron glomerular filtration rate and whole kidney glomerular filtration rate (GFR) are both reduced after 10 days of gentamicin therapy (23, 24). Aminoglycoside-induced impairment of the proximal tubule Na^+/H cotransport system leads to increased sodium delivery to the distal tubule, and this activates the tubuloglomerular feedback mechanism and the local release of angiotensin II. This would then play a regulatory role in modifying the final response in GFR.

The pathophysiological manifestations of nephrotoxicity occur at least 48 hours after cellular changes; the earliest changes are alteration in urine concentrating ability (25), proteinuria and enzymuria of tubular origin (26), and alteration in proximal tubular cell transport processes (27), including handling of acid load (28) and ammonium excretion. The proteinuria is due to alterations in glomerular permeability to lysozymes associated with decreased renal tubular reabsorption and degradation of lysozymes (26). Aminoglycoside-induced polyuria is associated with a defect in renal concentrating ability related to a decrease in inner medullary tonicity, and this is resistant to arginine vasopressin (25). Depression of GFR is a relatively late manifestation. The clinical threshold for toxicity is determined by the rate of cell necrosis and the rate of regeneration of proximal tubular cells (6).

The following sequence of events summarizes the mechanisms of aminoglycoside nephrotoxicity. The drug is filtered at the renal glomerulus and achieves high concentration in the tubular lumen (6), binding to apical cell membrane phosphoinositols (8, 14). This complex is pinocytosed into the cell, developing high intracellular concentrations; it becomes incorporated in lysozymes and inhibits phospholipid metabolism (9, 10). Interaction with

mitochondria leads to the generation of reactive oxygen metabolites that then may alter numerous cellular processes and cell function (16, 17). This may lead to impairment of cellular transport processes (27) and result in an increased distal tubular delivery of sodium that activates tubular glomerular feedback and a fall in glomerular filtration rate (23, 24).

AMPHOTERICIN B

Amphotericin B (AMB) is a polyene antibiotic containing a hydrophilic region, made up of an hydroxylated hydrocarbon chain, and a sequence of seven conjugated double bonds, which is lipophilic. This unique structure allows for the incorporation of the polyene molecule into cellular membranes and the alteration of membrane permeability (29). Following intravenous administration, AMB binds to sterol in most tissues, including cholesterol containing membranes, with the highest levels documented in the kidney (30). The route of elimination for amphotericin is unknown in humans. Although only 3% of a single intravenous dose appears in the urine after 24 hr, a greater percentage is detected after prolonged monitoring (31). This is important as it appears that for its nephrotoxic action on renal tubular cells, amphotericin needs to bind to the luminal membrane (32). AMB nephrotoxicity is manifested by changes in renal hemodynamics and alterations in renal tubular cell function. Acute infusions of AMB produced an early hemodynamic response which was maximal during infusion, with a fall in renal blood flow (RBF), GFR, and an increase in renal vascular resistance. This response persisted for 3 to 4 hr following cessation of the infusion (33). In studies where AMB is chronically administered, renal hemodynamics and tubule permeability are both altered in a way similar to the effects in an acute study, but to a lesser degree. It has been suggested that the smaller rise in vascular resistance may reflect an autoregulatory response modifying RBF and GFR (33). Experimentally, AMB produces extensive injury as evidenced by histological damage to the thick ascending limb of the loop of Henle. This injury is prevented by inhibition of active sodium transport with ouabain (34). The selective vulnerability of the thick ascending limb to anoxia results from its high transport activity, and reduced oxygen delivery (35) due to AMB-induced increases in renal vascular resistance (33). Ouabain did not modify the amphotericin-induced fall in RBF, and its protective effect is presumably mediated entirely by the decrease in oxygen demand for active transport (34). There appears to be a synergistic effect between the decrement in RBF and direct amphotericin membrane toxicity (34). Damage to the thick ascending limb leads to increased solute delivery to the distal tubule and macula densa, activating the tubuloglomerular feedback mechanism, leading to a fall in RBF and GFR (33, 36).

Andreoli (29) demonstrated the physicochemical interactions of AMB with membrane-bound cholesterol and other sterols that lead to the formation of aqueous pores and increased membrane permeability. In vitro, AMB increased brush border membrane permeability to sodium in a time-and-dose-dependent manner. Prolonged incubation of brush border membrane results in a generalized nonspecific increase in membrane permeability (37). The AMB-induced defect in acidification is characterized by a large increase in permeability for H^+ ions, and this impairs the cellular ability to maintain a pH gradient in the collecting tubule (33, 39). This is associated with increased potassium excretion (40). The invitro studies are consistent with the features seen clinically of an AMB-induced distal renal tubular acidosis (38).

The acute nephrotoxicity of amphotericin thus appears to be mediated by its effect on the luminal aspect of the tubular membrane (29, 32)—altering membrane permeability to small solutes (33, 37), modifying GFR and RBF acutely through increased solute delivery to the macula densa, and activating the tubuloglomerular feedback mechanism (33, 36). Amphotericin may also directly affect the glomerular mesangial cells, and the afferent or efferent arterioles, resulting in an almost immediate fall in RBF and a rise in renal vascular resistance. Chronic toxicity is due to a greater alteration in tubular membrane permeability and function (37), as well as to stimulation of active tubular transport in the thick ascending limb which increases oxygen demands in an hypoxic environment (34) due to the continuing increased renal vascular resistance (33).

In an attempt to reduce nephrotoxicity, AMB has been incorporated into liposomes as a carrier. Administration of this complex resulted in a marked reduction in nephrotoxicity in mice as well as in experimental clinical trials, due to alterations in the interaction of the polyene molecule with mammalian cell membranes. Amphotericin apparently does not transfer from liposomes to mammalian cells but does transfer effectively from donor liposomes to fungal cell walls, maintaining toxicity to fungi (41).

CEPHALOSPORINS

Cephalosporins contain the core nucleus of a 7-aminocephalosporanic acid to which various side chains are added to generate the semisynthetic cephalosporins. Cephalosporin selectively damages the S2 segment of the proximal tubule which is the major site of organic anion transport (42).

Nephrotoxicity is predominantly related to the intracellular concentrations of the various cephalosporins; and if high enough concentrations are generated, even transiently, then toxicity will ensue (42). The generation of high intracellular concentrations is dependent on several factors related to the chemical structure of the cephalosporins (43), the organic anion transport

system (42), and the degree of binding to intracellular receptors. Cephalosporin toxicity can be inhibited by the use of inhibitors of organic anion secretion or through competitive binding for intracellular target receptors by less toxic cephalosporins (44).

Cephaloridine is unusual, compared to other cephalosporins, because it undergoes active transport into the tubular cell at the basolateral membrane, but across the luminal membrane into the tubule, there is a failure of facilitated diffusion. The cationic charge on the pyridyl side ring results in transport of the compound by the organic base transport system on the luminal membrane which actively secretes the drug into the tubular lumen (45). Therefore, the high intracellular concentration of cephaloridine results from the very active anionic transport into the cell, the relatively minor active transport from the cell by the organic cation transport system, and then the almost imperceptibly facilitated diffusion at the luminal membrane (42). Cephaloridine appears to have a limited affinity for its intracellular molecular target, because it shows little or no cumulative toxicity when given in a series of marginally toxic doses. On the other hand, cephaloglycin will develop cumulative nephrotoxicity when given in a series of single daily nontoxic doses (42). Cephaloridine produces a sequence of events in the proximal tubular cell that are time related and dose dependent.

It is postulated that the pyridinium side chain of cephaloridine generates a superoxide via a redox cycle, catalyzed by cytochrome P-450 reductase and NADPH (43, 46). The superoxide ultimately leads to the formation of lipid peroxides. Lipid hydroperoxides are reduced to lipid alcohols by glutathione peroxidase, resulting in the oxidation of reduced glutathione (GSH) to oxidized glutathione (GSSG) (46). This requires the regeneration of NADPH via the pentose phosphate pathway to act as an electron donor for the reduction of GSSG to GSH by GSH reductase (46). Cephaloridine induces inhibition of gluconeogenesis and thus precedes the appearance of lipid peroxides (46); this only becomes apparent once NADPH stores are depleted (43, 46). This is followed by the depletion of renal cortical GSH concentrations (43). The degree of GSH depletion appears to be correlated with the magnitude of subsequent cortical injury (43). Thus, lipid peroxidation will not become evident until GSH levels are depleted. Cephaloglycin, however, lacks the pyridinium side ring but markedly inhibits mitochondrial function (44), which leads to cellular toxicity. Cephalothin, which does not have the pyridinium side ring, can also induce increased conjugated diene formation; this suggests free radical production and lipid peroxidation (47, 48). The cephalosporin toxicity may be mediated either by some as yet unexplained generation of a free radical, perhaps related to the 7-aminocephalosporanic acid ring, or more probably by a combination of several pathways.

CYCLOSPORINE A

Cyclosporine (CSA) is a neutral, highly lipophilic cyclic undecapeptide with a unique immunosuppressive action. It is now used extensively in solid organ and bone marrow transplantation. Nephrotoxicity (manifested as a rising serum creatinine and falling GFR, altered distal tubule function, and hypertension) has become the major recognized clinical problem with the use of cyclosporine. CSA has a high lipid solubility and is extensively distributed to extravascular tissues. CSA pharmacokinetics appear to fit a three-compartmental, open-distribution model with marked variation among individuals in absorption, metabolism, and elimination (49). Metabolism of CSA is via the cytochrome P-450–dependent mixed function oxidases, predominantly in the liver, and it generates either hydroxylated or N-demethylated metabolites (49).

In vitro studies show rapid uptake of CSA by proximal tubule segments and CSA binding to renal brush border membranes in a saturable fashion. An explanation of these findings may be that the lipophilic drug undergoes a partitioning process into the phospholipid phase of the membrane, rather than binding to a specific receptor (50).

Morphological studies of experimental CSA nephrotoxicity suggest early sublethal cellular damage confined to the S3 segments of the proximal tubule. The metabolism of CSA by the cytochrome P-450–dependent, mixed function oxidases, found predominantly in the cells of the S_3 segment, may possibly be involved in the pathogenesis of cellular damage (51, 52).

CSA may inhibit calmodulin-dependent phosphodiesterases, thus preventing the activation of protein kinases (53). Therefore, by binding to cellular and/or intracellular membranes, or to intracellular proteins, CSA has the potential to modify cellular function, and this may lead to cellular damage or alterations in cellular function. Acute infusions of CSA cause a dose-dependent functional alteration in renal vascular resistance (RVR), RBF, and GFR. These early changes are functional, with no evidence of structural damage, and are fully reversible following withdrawal of the drug (54, 55). The mechanisms of CSA-induced renal dysfunction are not clearly delineated, but evidence suggests that the increase in RVR is the functional change that leads to a fall in RBF and GFR.

CSA may enhance angiotensin II release or action directly, by stimulation of renin release (56), by interference with membrane receptors, or by changes in intracellular flux that lead to an increase in vascular resistance. Or it may do so indirectly by enhancing angiotensin II–induced sympathetic nerve activity and/or local catecholamine release. The acute hemodynamic effects of CSA can also be abolished by the concomitant infusion of prazosin, phenoxybenzamine, or renal denervation, suggesting that the

increase in RVR may in part be mediated by the renal sympathetic nervous system and/or circulating catecholamines (54). In addition, there is evidence that CSA modifies the production of vasodilatory and vasoconstricting prostaglandins, preventing an appropriate increase in protective vasodilating prostaglandins in response to angiotensin II vasoconstriction (57–59). If stimulation of the intrarenal renin-angiotensin system is not balanced by a concomitant rise in glomerular synthesis of prostaglandins, this may lead to changes in glomerular hemodynamics (60). Such changes appear to be due either to CSA's inhibiting of substrate release in the formation of prostaglandins (60) or to CSA's altering of phospholipase activity and modifying of the incorporation of arachidonic acid into the membrane pool, rather than to its effect on prostaglandin synthetase activity (61).

CSA nephrotoxicity is potentiated by ischemia (62, 63), and it is possible that the increased RVR, secondary to CSA, might prevent the increase in RBF required to promote resolution of the concurrent post ischemic renal injury (64).

Hyperkalemia and metabolic alkalosis are recognized side effects of CSA therapy. Contributing mechanisms are impaired hydrogen ion excretion, consistent with a voltage dependent distal renal tubular acidosis (65), and/or increased proximal tubular reabsorption of sodium and decreased potassium excretion (66).

The acute hemodynamic responses and subsequent tubular toxicity are probably linked. The S_3 segment is particularly vulnerable to hypoxic injury, which would be accentuated by hypoperfusion secondary to renal vasoconstriction and increased oxygen requirements for increased sodium reabsorption in the more distal nephron segments. The overall effect of these would be to potentiate the hypoxia and development of cellular damage.

Chronic CSA nephrotoxicity is becoming a recognized clinical state and is characterized by an irreversible and potentially progressive nephropathy (62; B. D. Myers, personal communication), as opposed to the acute nephrotoxicity characterized by no demonstrable cellular damage and reversible changes in RVR, RBF, and GFR. Hemodynamically, it is characterized by persistent elevation of RVR, a marked decline in GFR and RBF, a reduction in the filtration coefficient, and systemic hypertension. Histologically, it is characterized by a diffuse interstitial fibrosis or striped fibrosis (67) and by sclerosis of glomeruli.

CSA generates profound changes in the renal vasculature and has a direct effect on the renal tubule that leads to substantial changes in factors regulating vascular tone. CSA's effects are probably mediated through its lipid solubility which alters membrane structure and function. This interferes with the close interaction among the hormone receptor–mediated protein kinases and pro-

duces the alterations in renal vascular tone. The mechanisms have not yet been clearly elucidated.

ACETAMINOPHEN

Acetaminophen (APAP) is an effective analgesic and antipyretic agent that is freely available and widely used. It is the major active metabolite of phenacetin that has been used in compound analgesics and is implicated in the etiology of analgesic nephropathy (68). The handling of phenacetin and APAP exemplify the heterogeneity of renal anatomical, biochemical, and physiological characteristics that influence the development of renal toxicity. Phenacetin undergoes extensive first pass metabolism in the liver to APAP, and only small concentrations enter the systemic circulation. Phenacetin is filtered at the glomerulus and is passively reabsorbed in the nephron at a rate equivalent to water because of its lipid solubility (68, 69). APAP excretion involves filtration and reabsorption by passive diffusion of the non-ionic form. APAP is moderately lipid soluble. Clearance is independent of plasma concentrations or tubular reabsorption, which is not localized to a particular segment of the tubule (68, 69).

APAP accumulates in the medulla during antidiuresis. Diuresis results in an increased clearance, due to a change in the concentration gradient between intracellular/interstitial spaces and tubular fluid concentration. Phenacetin clearance is not altered by diuresis or antidiuresis, which is consistent with the failure of phenacetin to accumulate in the medulla (69). The development of APAP nephrotoxicity is linked to the proportional conversion of APAP to its toxic and nontoxic metabolites within the kidney. The generation of nontoxic conjugated APAP is potentially rate limited. Increases in APAP concentration will favor the generation of toxic metabolites (70).

The major enzymes involved in the metabolism of APAP are (*a*) the NADPH-dependent, cytochrome-P450 mixed function oxidases (MFO) located in the renal cortex and (*b*) the NADPH-independent prostaglandin endoperoxidase synthetase system (PGES), consisting of a fatty acid cyclo–oxygenase and prostaglandin hydroperoxidase, located predominantly in the inner medulla. The enzyme distribution appears to be central to the development of acute and chronic nephrotoxicity (70).

Acute Nephrotoxicity

Acute nephrotoxicity occurs clinically in the context of an acute overdose of APAP, often but not always associated with hepatic toxicity (71). The metabolism of APAP to a reactive arylating metabolite is requisite for the development of acute tubular necrosis, with the histological lesion confined predominantly to the renal cortex (71, 72). These same authors showed that

APAP can be deacetylated to p-aminophenol (PAP), and that PAP is 5–10 times more nephrotoxic than APAP. The PAP undergoes autooxidation or oxidation by cytochrome P-450 MFO or PGES. The concentration of APAP in the kidney is important in the development of acute toxicity. In the acute overdose situation, the high concentrations cannot be handled by the cytochrome P450 system, and GSH stores are rapidly depleted in the renal cortex. The formation of arylating intermediates following deacetylation of APAP would lead to arylation of renal macromolecules, which Newton and colleagues postulate as the initiating event in APAP acute tubular necrosis (72).

Thus, there are three biochemical pathways for the generation of a radical intermediate: the first is mediated by cytochrome P-450 MFO; the second by PGES; and the third by deacetylation, followed by oxidation of either one or two of the metabolites formed.

Chronic Toxicity

APAP reaches a high concentration within the cells of the renal inner medulla in comparison with the cells of the renal cortex and plasma. This concentration gradient correlates with the extent of protein covalent binding of APAP within the kidney (70). The PGES-mediated pathway activating APAP is predominant in the renal inner medulla and appears to be the main mediator of chronic APAP nephrotoxicity. Prostaglandin synthesis in the rabbit inner medulla is stimulated at low concentrations and inhibited by APAP at extremely high concentrations. Therefore, since concentrations achieved during chronic abuse do not exceed 0.5 mM APAP (70, 73), APAP activation would be enhanced in this situation. The conversion of APAP to its reactive intermediate by PGES probably involves a one electron oxidation reaction and hydrogen abstraction to form the phenoxy radical of APAP which, in turn, may be further oxidized to N-acetyl-p-benzoquinoneimine (NAPQI), prior to reaction with GSH (74). The rapid reaction of NAPQI with GSH could cause severe depletion of intracellular GSH by similar reactions in the renal inner medulla, which has the lowest concentration of GSH (73). The extent of co-oxidative activation of APAP mediated by PGES is related to the activity of glutathione peroxidases. Since PGES, as opposed to glutathione peroxidase, does not require GSH for substrate, depletion of GSH would decrease glutathione peroxidase participation and increase PGES activation, with the resultant increase in cooxidation of APAP (73).

GSH concentration is critical in preventing the covalent binding to renal macromolecules by the reactive APAP metabolites. The metabolite NAPQI is reduced back to its parent compound, and GSSG is then recovered intracellularly by glutathione reductase. GSSG recovery is impaired in the renal

inner medulla due to the low activity of glutathione reductase and the possible lack of NADPH. In addition, extracellular GSSG is not readily available to the renal inner medulla cells, due to the very low levels of gamma glutamyl transpeptidases on the cell membranes (73). The net effect is an increased sensitivity of the renal inner medulla to the nephrotoxic effects of APAP at low concentrations.

Compound analgesics containing aspirin and phenacetin have a synergistic effect in the development of chronic nephrotoxicity. Therapeutic concentrations of APAP will stimulate PGES activity and lead to increased activation of APAP. Aspirin has a modest inhibitory effect on the cycloxygenase component of PGES, but no effect on the PG hydroperoxidase activity. Aspirin is deacetylated to salicylate, which then competes with aspirin for cellular uptake, but more importantly, salicylate has been shown to have a potent effect in depleting renal glutathione levels. Thus, the reactive intermediate of APAP has an increased capacity for covalent binding to renal macromolecules and for initiating cellular toxicity (68, 73).

CONCLUSION

We have reviewed in detail several drugs that highlight the role of the kidney's unique functional organization in the development of nephrotoxicity. Researchers in this field have expanded our understanding of the renal mechanisms involved in the etiology of drug nephrotoxicity. The rate of renal blood flow may, in a limited number of instances, influence the effect of a drug on renal function. In turn, renal blood flow may be modified in response to drug toxicity. However, it is the heterogeneity of the renal tubular epithelial cells' function and metabolism that is the major determinant in the development of nephrotoxicity.

Cellular metabolism and the generation of toxic metabolites are dependent on the intrarenal distribution of specific enzyme systems (cf cytochrome P-450 MFO in the renal cortex with the prostaglandin endoperoxidase synthetase predominantly in the renal medulla). The concentration of the drug and/or its metabolites within the cell plays a critical role in the generation of toxicity. This is modified by the tubular reabsorption and secretion of the drug and also by the availability of enzyme substrates that are important in maintaining cellular integrity and cellular repair mechanisms.

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