Furosemide and Dexamethasone as risk factors for neonatal nephrocalcinosis

"A Systematic review"

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By
Ahmed Salah ElDin Sayed
M.B,B.Ch.
Faculty of medicine
Cairo university

Supervised by
Prof.Dr.
Fatina Ibrahim Fadel
Professor of Pediatrics
Faculty of medicine
Cairo university

Prof.Dr.
Lamiaa Mohamed Mohsen
Professor of Pediatrics
Faculty of medicine
Cairo university

Prof.Dr.
Hafez Mahmoud Bazaraa
Ass. Professor of Pediatrics
Faculty of medicine
Cairo university

Faculty of medicine
Cairo university
2008

Abstract

Nephrocalcinosis is a fairly common finding especially among preterm neonates. Dexamethasone and furosemide are two of the proposed risk factors for neonatal nephrocalcinosis. Furosemide is mainly used in neonates in cases of heart failure, PHVD and in CLD. Dexamethasone is used mainly in the treatment of CLD. Aiming to determine whether these two drugs are risk factors for neonatal nephrocalcinosis, in this systematic review a search was done to identify studies addressing the cause-effect relationship between the use of such drugs and nephrocalcinosis. Then, eligible studies were analyzed. Review of the included studies supports the association between both furosemide and dexamethasone therapy in neonates and the development of nephrocalcinosis. Clinicians should balance the benefits and harms of the use of these drugs in neonates. More studies should focus on the incidence, causation and prognosis of nephrocalcinosis.

Key Words :

Furosemide – Dexamethasone – Neonate – Nephrocalcinosis.

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Abbreviations

ACZ acetazolamide

BPD bronchopulmonary dysplasia

CLD chronic lung disease

CSF cerebro-spinal fluid

DEX dexamethasone

FUR furosemide

IPPV intermittent positive pressure ventilation

LP lumbar puncture

NC nephrocalcinosis

PHVD post-hemorrhagic ventricular dilatation

PHH post-hemorrhagic hydrocephalus

PDA patent ductus arteriosus

PMN polymorph-nuclear

RCT randomized controlled trial

RDS respiratory distress syndrome

U/S ultrasound

VLBW very low birth weight

V-P ventriculo-peritoneal

Introduction and aim of the work

There has been a growing concern about the factors predisposing to nephrocalcinosis in neonates. Nephrocalcinosis is defined as an increase in the calcium content of the kidney.*(Ronnefarth et al.,2000)*. The presence of neonatal nephrocalcinosis was first described by *Hufnagle et al in 1982*.

Nephrocalcinosis is not a uniform entity but rather a complication of various renal disorders, metabolic disturbances or the application of drugs. It has been associated with the later impairment of glomerular and distal tubular function.*(Schell-Feith et al.,2003.*

Nephrocalcinosis is detected sonographically by hyperechogenecity of the medullary renal pyramids after exclusion of other causes of such finding.*(Saarela et al.,1999)*

Concerning risk factors for neonatal nephrocalcinosis , it was found that -in general- it develops as a result of an imbalance between stone-inhibiting and stone-promoting factors. A high intake of calcium, phosphorus, and ascorbic acid, a low urinary calcium/citrate ratio, a high urinary calcium/creatinine ratio, immaturity and medication to prevent or treat chronic lung disease with hypercalciuric side effects appear to contribute to the high incidence of nephrocalcinosis in preterm neonates.*(Schell-Feith et al.,2000)*. These drugs include among others dexamethasone and furosemide. They are widely used in certain neonatal conditions for example: Bronchopulmonary dysplasia and for prevention of post-hemorrhagic hydrocephalus. Dexamethasone has been shown to

lower the incidence of chronic lung disease in a number of studies and meta-analyses. Acetazolamide and furosemide therapy was found to be useful in the treatment of preterm infants with post-hemorrhagic hydrocephalus and elevated intracranial pressure, allowing a significant proportion to avoid ventricular shunting procedures.*(Libenson et al.,1999)*.

Owing to the above mentioned potential effect of nephrocalcinosis on the overall renal function, in addition to the lack of conclusive evidence regarding the effect of such commonly used drugs ; the present study aims to identify the risk factors of neonatal nephrocalcinosis according to the current best evidence from research and -in doing so- weigh the advantages and disadvantages of using such drugs.

The present study is a systematic review. Systematic reviews have several advantages including:

- The methods applied in appraisal of clinical studies help limit bias in identifying and rejecting studies.
- Meta-analyses increase the accuracy of the overall result.
- Inconsistency in results in different studies can be identified and new hypotheses regarding different subgroups reached.

In order to able to conduct a systematic review the current literature regarding the etiology and risk factors of neonatal nephrocalcinosis will be reviewed . A search will be conducted aiming to identify studies addressing the cause-effect relationship between the use of drugs such as furosemide and dexamethasone in neonates and nephrocalcinosis.

Background

Furosemide:

Furosemide is one of the loop diuretics. Loop diuretics are a chemically diverse group, where both Furosemide and Bumetanide contain a sulfonamide moiety.

Furosemide is an inhibitor of Na^+ - k^+ - $2cl^-$ symport acting primarily in the thick ascending limb.

The flux of Na^+, k^+ and Cl^- from the lumen into the epithelial cells in the thick ascending limb is mediated by a Na^+ - K^+ - $2Cl^-$ symporter *(Hebert, 1999)*. This symporter captures the free energy in the Na^+ electrochemical gradient established by the basolateral Na^+ pump and provides for transport of K^+ and Cl^- into the cell. The luminal membranes of epithelial cells in the thick ascending limb have a large conductive pathway for K^+ ; therefore, the apical membrane voltage is determined by the equilibrium potential for K^+ (EK) and is hyperpolarized . In contrast, the basolateral membrane has a large conductive pathway for Cl^-, so the basolateral membrane voltage is less negative than EK. This results in a trans-epithelial potential difference of approximately 10 mv, with the lumen positive with respect to the interstitial space. This lumen positive potential difference repels cations driving them into the interstitial space.*(Murad et al.,2006)*

Therefore, inhibitors of Na^+ - K^+ - 2 Cl^- symport also inhibit Ca^{2+} and Mg^{2+} reabsorption in the thick ascending limb.*(Isenring and Forbush, 1997)*

Effects on urinary excretion:

Furosemide increases the urinary excretion of Na^+ and Cl^- profoundly (i.e up to 25% of the filtered load of Na^+). Also it increases the urinary excretion of Ca^{2+}, Mg^{2+}, K^+ and titratable acid. Furosemide has a weak carbonic anhydrase–inhibiting activity which increases the urinary excretion of HCO_3^- and phosphate. Acutely furosemide increases the excretion of uric acid whereas chronic administration results in reduced excretion of uric acid.*(Wilcox,1999)*

Effects on renal hemodynamics:

Furosemide increases total renal blood flow and redistributes renal blood flow to the midcortex.

Loop diuretics are powerful stimulators of renin release .This effect is due to interference with NaCl transport by the macula densa and, if volume depletion occurs, to reflex activation of the sympathetic nervous system and to stimulation of the intrarenal baroreceptor mechanism. Prostaglandins, particularly prostacyclin, may play a role in mediating the renin-release response to loop diuretics. *(Murad et al.,2006)*

Other actions:-

The administration of furosemide acutely increases lung compliance and reduces airway resistance. It may also facilitate a reduction in ventilator requirements and cause transient improvements in blood gases in both ventilated and non ventilated babies. (Rennie et al., 1999).

Furosemide increases systemic venous capacitance and thereby decreases left ventricular filling pressure. This effect is

mediated by prostaglandins and requires intact kidneys. It benefits patients with pulmonary edema even before diuresis ensues. *(Murad et al.,2006)*

In vitro, high doses of furosemide can inhibit electrolyte transport in many tissues. For instance, alterations in the electrolyte composition of endolymph in the inner ear contribute to drug induced ototoxicity. Furosemide also may inhibit Na^+- K^+ - ATPase, glycolysis, mitochondrial respiration, the microsomal Ca^{2+} pump, adenyl cyclase, phosphodiesterase, and prostaglandin dehydrogenase, however, these effects do not have therapeutic implications. *(Murad et al.,2006)*

Absorption and elimination:

Furosemide is bound extensively to plasma proteins; its delivery to the tubules by filtration is limited. However, it is secreted efficiently by the organic acid transport system in the proximal tubule and thereby gains access to its binding sites on the Na^+ - K^+ - $2Cl^-$ symport in the luminal membrane of the thick ascending limb.

Approximately 65% of furosemide is excreted unchanged in urine and the remainder is conjugated to glucuronic acid in the kidney. Accordingly, in patients with renal but not liver disease, the elimination half-life of furosemide is prolonged.

Oral bioavailability of furosemide varies from 10% to 100%.

All loop diuretics have short elimination half-lives and prolonged release preparations are not available. Consequently, often the dosing interval is short so as to maintain adequate levels of loop diuretics in the tubular lumen. As the concentration of loop

diuretic in the tubular lumen declines, nephrons begin to reabsorb Na^+ which nullifies the overall effect of the loop diuretic on total body Na^+. This can be overcome by more frequent administration of the loop diuretic or by restricting dietary Na^+ intake. *(Ellison et al., 1999).*

Toxicity, adverse effects, contraindications, drug interactions:

Most adverse effects are due to abnormalities of fluid and electrolyte balance.

Overuse of loop diuretics can cause serious depletion of total body Na^+. This may manifest as hyponatremia and/or extracellular fluid volume depletion associated with hypotension, reduced GFR, circulatory collapse, thromboembolic episodes and in patients with liver disease, hepatic encephalopathy. Increased delivery of Na^+ to the distal tubule particularly when combined with activation of the renin-angiotensin system leads to increased urinary excretion of K^+ and H^+, causing a hypochloremic alkalosis. If dietary K^+ intake is not sufficient, hypokalemia may develop and this may induce cardiac arrhythmias particularly in patients taking cardiac glycosides. Increased Mg^{++} and Ca^{++} excretion may result in hypomagnesemia (a risk factor for cardiac arrhythmias) and hypocalcemia. *(Murad et al.,2006)*

Furosemide can cause ototoxicity that manifests as tinnitus, hearing impairment, deafness, vertigo and a sense of fullness in the ears. Hearing impairment and deafness are usually reversible. Ototoxicity occurs most frequently with rapid intravenous

administration and least frequently with oral administration. *(Murad et al.,2006)*

Other side effects include increasing plasma levels of LDL, while decreasing plasma levels of HDL, hyperglycemia, hyperuricemia, skin rashes, photosensitivity, parathesia, bone marrow depression, hypersensitivity to sulfonamides and anuria unresponsive to a trial dose of loop diuretic. *(Murad et al.,2006)*

Drug interactions:-

1- Aminoglycosides: synergism of ototoxicity.

2- Anti-coagulants: increased anticoagulant activity.

3- Digitalis glycosides: increased digitalis induced arrhythmias.

4- NSAIDs : blunted diuretic response.

5- Thiazide diuretics: synergism of diuretic effect of both drugs leading to profound diuresis.

Therapeutic uses:-

- In the treatment of acute pulmonary edema. A rapid increase in venous capacitance in conjunction with a brisk natriuresis reduces left ventricular filling pressure and thereby rapidly relieves pulmonary edema.

- In the treatment of chronic congestive heart failure when diminution of extracellular fluid volume is desirable to minimize venous and pulmonary congestion.

- In the treatment of hypertension, loop diuretics lower blood pressure as effectively as thiazides while causing small perturbations in the lipid profile. *(Van Der Hejiden et al., 1998).*

- To reduce the edema of nephrotic syndrome which is often refractory to other classes of diuretics.

- In patients with a drug overdose to induce a forced diuresis to facilitate more rapid renal elimination of the offending drug.

- Also furosemide is used with hypertonic saline for the treatment of life threatening hyponatremia. Patients with acute renal failure receive a trail dose of a loop diuretic in an attempt to convert oliguric ARF to non oliguric ARF. *(Murad et al.,2006)*

Furosemide in neonates:

In neonates, the onset of action of intravenous furosemide occurs within 5 minutes with peak activity at 20 to 60 minutes and a duration of action of approximately 2 hrs. The bioavailability of oral furosemide is less than 20%. At least 94% of plasma furosemide is protein-bound. *(Kao and Durand, 1991).*

In infants who weigh less than 1,250g, furosemide elimination occurs primarily by glomerular filtration. However, by the time infants reach 40 weeks post conception the predominant pathway of elimination may be by the proximal convoluted tubules. The half-life of plasma furosemide in the first 6 weeks of life ranges from 8 to 20 hours. *(Kao and Durand, 1991).*

Mechanism of action:

In addition to the renal effects discussed before, furosemide has a direct pulmonary vasoactive effect causing increased venous capacitance, increased oncotic pressure, decreased pulmonary microvascular fluid filtration rate, and increased lymphatic flow. This will lead to a decrease in fluid filtration into the pulmonary interstitium. Furosemide has also been shown to

decrease Vasopressin which is often elevated in infants with BPD. *(Kao and Durand, 1991).*

Therapeutic uses of furosemide in neonates:

A study by *Rennie et al* in 1999 showed a rapid short term improvement in pulmonary function in infants recovering from BPD following a single intravenous dose of furosemide (1 mg/ Kg body weight). Within 1 hour of treatment, airway resistance decreased 36% and dynamic compliance increased 54%. By 6 hours both compliance and resistance had returned to their baseline values. Another study by *Engelhardt et al* in 1986 showed that long-term diuretic therapy can improve the mechanical properties of the lungs of spontaneously breathing infants with BPD.

Furosemide is used in the management of congestive heart failure in neonates. Causes of heart failure in preterm neonates include fluid overload, PDA, VSD and cor-pulmonale resulting from BPD. As for the full-term neonate, causes are myocarditis, some of the congenital heart diseases and A-V malformations.

Furosemide was used in combination with acetazolamide for the prevention of post hemorrhagic hydrocephalus of the newborn. *Libenson et al* in 1999, evaluated the efficacy of this combination in avoiding ventricular shunting procedures in preterm infants with post-hemorrhagic hydrocephalus and increased intracranial pressure.

Side effects:

1-Furosemide causes enhanced excretion of water, calcium, phosphate, magnesium, sodium, potassium, chloride and bicarbonate. Hypokalemia, hyponatramia and hypochloremia can