Biochemical Changes Associated with Intravenous Use of Contrast Media

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ABSTRACT

Introduction: The general indication for the use of iodinated contrast media (CM) is to create an X-ray attenuation differential in tissues in order to increase the visualization of the disease process. The use of CM can be associated with clinical and biochemical effects some of which may be harmful e.g. contrast induced nephropathy, haemodynamic alterations and idiosyncratic reactions amongst others. This hospital-based prospective analytical study investigated biochemical derangements associated with the use of contrast media.

Methods: One hundred and eighty consenting adult patients who received intravenous contrast media during radiological investigations at the University of Benin Teaching Hospital, Edo State, Nigeria were recruited over a 6-month period. Data on their socio-demographic characteristics and health status were collated. Venous blood was collected pre- and up to 72 hour- post contrast studies to measure for serum electrolytes, urea, creatinine and albumin. Urine was similarly collected and examined using dipsticks for abnormalities.

Results: The mean serum sodium and potassium decreased significantly from baseline values after 24hours, while the mean serum urea, creatinine and urine pH increased. These changes returned to normal by 72hrs post contrast exposure, except for one patient who required haemodialysis. Fifty-one (51) out of 142 patients developed CIN defined as elevation of serum creatinine by ≥ 25%, 24-72hrs after exposure to contrast.

Conclusion: Intravenous use of contrast media is associated with significant but mostly transient biochemical derangements. A longer follow-up is however required to possibly exclude future deleterious outcome.

INTRODUCTION

Iodinated contrast media (CM) are among the most commonly prescribed medications in the history of Medicine, with approximately 80 million doses being administered in 2003 worldwide corresponding to 8 million litres [1]. The general indication for the use of iodinated CM is to create an X-ray attenuation differential in tissues in order to increase the visualization of the disease process. In the last two decades the use of CT scan has increased by 800% [1, 2]. From 1979 to 2005, the number of cardiac catheterization procedures in the United States of America increased 4.5 fold [3]. We can similarly infer that the use of CT scan in developing countries has increased over the years although these equipments are still very much in short supply compared to the demand for their use.

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Generally CM are classified into ionic or non-ionic and as monomers or dimers. Non-ionic CM have the desirable property of being water-soluble and yet do not dissociate in water [4]. The earliest agents were ionic with extremely high osmolality of about 2000 mOsm/L; these were predominant until the 1980s when the non-ionic agents with a lower osmolality of 600-900 mOsm/L were introduced. CM can also be classified based on osmolality, into low osmolality contrast media (LOCM) and high osmolality contrast media (HOCM) [1, 4]. LOCM are further divided into hypo-osmolar and iso-osmolar.

LOCM are preferred CM for patients undergoing IVU and CT, especially for those with increased risks such as diabetic nephropathy a. The first LOCM in clinical use was Ioxaglate. It is both ionic and also the first dimer in clinical use. Other LOCM include iohexol, ioverso, and iopromide amongst others. Non-ionic dimers with lower osmolality have been produced; iodixanol is the only agent in this class available for intravenous use and is iso-osmolar to blood at all iodine concentrations. It is referred to as iso-osmolar contrast media (IOCM) [4]. Iso-osmolar CM have been reported to cause more proximal tubular cell vacuolization, erythrocyte aggregation and cessation of blood flow in the renal microcirculation [5].

Another classification of CM was proposed by the European Society of Urogenital Radiology guideline based on risk of nephrogenic systemic fibrosis (NSF) i.e. high, intermediate and low risk of NSF[6]. NSF is a rare scleroderma like condition that affects patients with renal insufficiency, which has been, associated with the use of gadolinium-containing contrast agents (particularly gadodiamide and gadopentetic acid).

Intravascular iodinated CM quickly transits the capillary pores into the interstitial, extracellular space and into the renal tubules through glomerular filtration [7]. In normal patients, the kidney eliminates almost all of the contrast media while extra-renal routes like the liver and bowels only excrete about 1%. This may be more in patients with renal insufficiency.

The use of CM can be associated with clinical and biochemical effects some of which may be harmful like chemotoxic and anaphylactoid reactions. The properties of CM that potentially contribute to their toxicity include whether they are ionic or non-ionic, iodine content, osmolality, viscosity and other physicochemical properties [8,9].

Contrast media cause biochemical derangements, some of which were reported by Nzeh *et al* in 1994 [10]. Decreases in serum electrolytes, calcium and proteins in patients undergoing intravenous urography was observed in the study and these biochemical alterations, especially that of calcium was said to be responsible for the cardiac arrhythmia complicating CM injection[10]. Consistently low urinary sodium and fractional excretion of sodium was observed in 12 patients with CIN, a finding that would be consistent with either decreased renal perfusion or acute tubular obstruction [11]; as has been previously documented [12]. Data has however been inconsistent, as other groups have reported natriuresis and an increase in fractional excretion [13, 14]. Some studies [15,16,17] have reported on the effects of contrast media on various urinary enzymes and markers of glomerular and tubular function such as N-acetyl-□-D-glucosaminidase, γ-glutamyl transpeptidase, alkaline phosphatase, 3-nitrotyrosine, β2-microglobulin, adenosine deaminase binding protein, albuminuria and proteinuria. Pollard, *et al* [18] reported no biochemical alterations following intravenous injection of three types of contrast (ionic iodinated, non-ionic iodinated and gadolinium) in anaesthetised rats.

Studies from developing countries on the clinical or biochemical effects of CM use are limited. This hospital-based prospective analytical study investigated some biochemical derangements associated with the use of contrast media.

MATERIALS AND METHODS

The study was conducted in the University of Benin Teaching Hospital (UBTH), a tertiary hospital in the South-South region of Nigeria that serves as the main referral hospital in the region. All consenting adult inpatients and outpatients referred to the Radiology department for contrast enhanced computed tomography scans or intravenous urography (IVU) were recruited consecutively over a period of 6 months.

Patients excluded from the study were those with ESRD/ On maintenance haemodialysis, uncontrolled hyperthyroidism/ thyroid malignancies,

NYHA class IV CCF, history of hypersensitivity to contrast or exposure to contrast in the last 24-48hr and nursing/pregnant subjects.

Iopamidol, a low osmolar non-ionic iodinated CM was injected intravenously for patients who had CT scans while diatrizoate (urograffin), a high osmolar CM was used for IVU. All patients referred for IVU in the study centre are by protocol required to present a recent serum creatinine result, this was not strictly so for CT scan. However for patients in whom benefits of the procedures outweigh the risks, they are scanned regardless. No hydration protocol was performed.

Five mls of venous blood was collected by venepuncture (before, 24, 48 and 72 hours after exposure to contrast media) into lithium heparin bottles for serum electrolytes, urea and creatinine estimation. Creatinine estimation was done using the modified Jaffe's method [19], while glomerular filtration was estimated using CKD EPI [20]. Five mls of blood was also collected into EDTA bottles and plain bottles for haematocrit and serum albumin estimation respectively. Random urine samples were collected into plain bottles and tested using the 10-parameter multistix (Medi-Test Combi 10® SGL by Macherey-Nagel) for urinary abnormalities before and up to 72 hours after exposure to contrast media for evidence of urinary abnormalities e.g. proteinuria, haematuria

RESULTS

One hundred and forty-two patients completed the study. Of the 142 patients 17 (12%) were outpatients while 125(88.0%) were inpatients /emergency patients. One hundred and thirty three patients were referred for CT scan while only 9 had IVU. Age of subjects ranged between 18-85years. There were more males than females with a sex ratio of 1:1.6 (F: M). Among the patients, 9.9% were hypertensive, 7.0% diabetic, 22.5% and 4.2% respectively had family history of hypertension and diabetes, 2.1% had a history of diagnosed renal disease, 26.1% used alcohol and 6.3% smoked.

The mean serum sodium , potassium and mean eGFR decreased from baseline values after 24hours, while the mean serum urea, creatinine and urine pH increased. These differences were all statistically significant (Table 1). Fifty-one patients (35.9%) developed CIN (elevation of serum creatinine by $\geq$ 25%, 24-72hrs after exposure to contrast) and of this only one patient required haemodialysis with renal function returning to normal baseline within 2 weeks. One of the 9 (11.1%) patients who had IVU and 50 out of 133 (37.5%) who had CT scan developed CIN (p=0.150†), while 17.6% and 38.4% of outpatients and inpatients respectively developed CIN (p=0.160).

Table 1: Comparison of baseline biochemical parameters at baseline and 24hour after

Parameter	Before Mean ± SD	24hr After Mean ± SD	Mean Difference (95% CI)	P Value
Serum sodium (mmol/L)	137.3 ± 5.8	136.3 ± 6.75	1.0 (0.3, 1.8)	0.009*
Serum potassium (mmol/L)	3.8 ± 0.6	3.7 ± 0.6	0.1 (0.1, 0.2)	0.027*
Serum bicarbonate (mmol/L)	22.3 ± 4.1	22.2 ± 3.7	0.1 (-0.4, 0.5)	0.792
Serum chloride (mmol/l)	102.9 ± 11.5	104.5 ± 6.4	-1.6 (-4.3, 1.1)	0.228
Serum Urea (mg/dl)	41.2 ± 24.9	44.6 ± 31.7	-3.4 (-6.1, -0.6)	0.016*
Serum Creatinine (mg/dl)	0.9 ± 0.5	1.1 ± 0.6	-0.2 (-0.3, -0.2)	< 0.001*
eGFR (ml/min)	109.3 ± 32.6	92.1 ± 36.2	17.2 (13.1,21.4)	<0.001*
Urine pH	6.0 ± 0.8	6.3 ± 0.7	-0.3 (-0.4, -0.2)	< 0.001*
Serum Albumin (g/dl/)	3.6 ± 0.5	3.5 ± 2.5	0.1 (0.3, 0.5)	0.652

SD - Standard deviation, CI - Confidence interval, eGFR- estimated glomerular filtration rate

Table 2: Baseline urinary abnormalities for CIN (+) and CIN (-) patients

Urinary finding	CIN (+) n(%) or mean ± SD	CIN (-) n(%) or mean ± SD	P value
Proteinuria (n=39)	17(33.3)	22(24.2)	0.241
Haematuria (n=27)	11(21.6)	16 (17.6)	0.561
pH	5.82 ± 0.71	6.15 ± 0.86	0.021*
Specific gravity	1.022 ± 0.006	1.019 ± 0.007	0.190

Table 3: Comparison of baseline biochemical parameters for CIN (+) and CIN (-) patients

Parameters in serum	**CIN (+) Mean ± SD**	**CIN (-) Mean ± SD**	**Mean Difference (95% CI)**	**P value**
Sodium (mmol/L)	138.29 ± 5.69	136.67 ± 5.94	1.6 (-0.3, 3.6)	0.115
Potassium (mmol/L)	3.79 ± 0.65	3.83 ± 0.56	-0.0(-0.2, 0.2)	0.716
Bicarbonate (mmol/L)	21.76 ± 3.79	22.56 ± 4.31	-0.8(-2.2, 0.6)	0.273
Chloride (mmol/L)	101.88 ± 6.43	100.09 ± 11.28	1.7(-1.7, 5.3)	0.317
Urea (mg/dl)	52.76 ± 33	34.75 ± 15.48	18.0 (9.9, 26.1)	< 0.001*
Creatinine (mg/dl)	0.96 ± 0.68	0.84 ± 0.27	0.1(0.0, 0.3)	0.143
Albumin (g/dl)	3.50 ± 0.51	3.63 ± 0.49	-0.1 (-0.3, 0.1)	0.163

At baseline, a higher proportion of CIN (+) patients had proteinuria and haematuria compared to CIN (-) patients, this difference was not statistically significant. Urine pH was significantly lower among CIN(+) patients (Table 2).

The mean urea was significantly higher in CIN (+) than CIN (-) patients. Mean serum creatinine was higher and serum albumin lower in the CIN (+) than the CIN (-) patients, but these differences were not statistically significant (Table 3).

DISCUSSION

Our study confirms the decrease in mean serum sodium and potassium concentration 24 hours post-exposure to contrast, this finding is consistent with what was reported by Nzeh *et al* [10] and can be explained by hemodilution. Although we report that the mean serum albumin reduced 24 hours post-contrast this difference was not statistically significant. Other studies have reported a reduction of these biochemical parameters within 24 hours of exposure to contrast. Brunet *et al* reported similar findings, ascribing the reduction in sodium and potassium to haemodilution; the decrease in serum calcium and albumin were greater but difficult to explain [21]. The study by Kokkas *et al* reported

that there was no influence of iohexol, a non-ionic LOCM, on electrolytes and protein [22]. Similarly Pollard *et al* [11] found no biochemical alterations in serum following intravenous injection of 3 types of CM.

Although there was a significant decline in eGFR within 24hrs, this change occurred acutely in an unsteady haemodynamic state and one should be cautious in interpreting this as clinically relevant reduction in renal function. Previous studies monitored serum electrolytes at 5mins, 30mins, 60mins and 24 hours post contrast and some parameters were found to be returning to baseline values within 24 hours [21, 22]. In the present study, electrolytes were measured after 24 hours and parameters returned to normal by 72 hours for majority.

We report an overall frequency of CIN of 35.9% and this was lower among our outpatient subset (17.6%). Possible reasons for our observations and the risk factors for CIN have been discussed in earlier publications [23]. Expectedly mean serum urea was higher at baseline in the patients who developed CIN. Raised serum urea may have been an indication of dehydration, which is a risk for CIN.

Prior to contrast exposure proteinuria and haematuria were more prevalent among patients who developed CIN than those who did not, though this did not reach statistical significance. Changes observed in urine such as proteinuria and pH changes, within 24hours of contrast injection are usually as a result of the presence of contrast media in urine. It causes changes in urine pH and results in false positive proteinuria [24]. Changes in urine parameters occurring within 24 hours following contrast exposure should be interpreted with caution.

The present study was limited by a high dropout rate especially among outpatients due to unavailability for follow up blood draws; also death or discharge of inpatients. Not all biochemical parameters were measured due to cost implications. Though we report transient biochemical derangements, our patients were not followed up long enough to certainly exclude future biochemical changes that may be related to contrast exposure.

CONCLUSION

Intravenous use of contrast media is associated with significant but mostly transient biochemical derangements including decreased serum sodium, potassium and increased serum urea, creatinine and urine pH**.** A longer follow-up is however required to establish the long-term consequences of these alterations.

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