

A MULTI-CASE REPORT OF ACUTE RENAL FAILURE IN PATIENTS TREATED WITH AGGRENEX®

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ABSTRACT

Background

Aggrenox® is used in the secondary prevention of stroke. Acute renal failure, potentially associated with Aggrenox®, has been observed in several patients.

Objective

The objective of this study was to determine if Aggrenox® was associated with acute renal failure and to determine whether it was acetylsalicylic acid, dipyridamole or the combination that led to decline in renal function.

Methods

A case series of three patients suffering severe nausea, vomiting, diarrhea, renal dysfunction and clinical decline during Aggrenox® therapy was examined. Serum creatinine and Blood Urea Nitrogen (BUN) were measured to evaluate renal function.

Results

Analysis of this patient group revealed that Patient 1 experienced nausea, emesis, anorexia, diarrhea and significant clinical decline during treatment with Aggrenox®. Patients 2 and 3 also presented with complaints of nausea and emesis. Lab measurements along with clinical symptoms indicated that all three patients experienced acute renal failure, having increases in serum creatinine of 186%, 144% and 249%, respectively. Symptoms and lab work returned to baseline following discontinuation of Aggrenox®.

Conclusion

It is biologically plausible that Aggrenox® may contribute to renal dysfunction in patients under certain pathophysiological circumstances.

Keywords: *Clinical pharmacology; Aggrenox®; Dipyridamole; acetylsalicylic acid; acute renal failure*

Aggrenox®, a combination of acetylsalicylic acid (ASA) and dipyridamole, has proven effective in the secondary prevention of ischemic stroke.¹ By irreversibly inhibiting cyclo-oxygenase, ASA prevents the formation of thromboxane A₂ which is a platelet aggregation inducer and vasoconstrictor.²⁻⁴ Dipyridamole inhibits the transport and metabolism of adenosine resulting in elevated local concentrations of adenosine.⁵ Discussions on the mechanism of dipyridamole often focus on elevated adenosine in relation to platelets and the vasodilatory affect on the coronary

vasculature; however, the effects of dipyridamole are not limited to platelets and adenosine is not always a vasodilator.^{6,7}

In most organs, adenosine produces arteriolar vasodilation, but in the kidney, elevated levels of adenosine lead to arteriolar vasoconstriction. This results in a reduced glomerular filtration rate (GFR), which is an indicator of reduced renal function.⁶⁻¹⁰ Hall and Granger suggest a possible mechanism for this from their findings in a 1986 study. Their results indicate that adenosine markedly alters the control of GFR by angiotensin II, possibly causing angiotensin

II to constrict preglomerular vessels. In other words, adenosine enhances the responsiveness of preglomerular vessels to angiotensin II.⁸ Llach and colleagues found that dipyridamole induced marked and reversible decreases in renal perfusion flow and GFR in cirrhotic patients with ascites and an overactive renin-angiotensin system.¹¹ Nuclear medicine techniques have shown similar results including the determination that dipyridamole administration leads to a reduced GFR in otherwise healthy individuals.¹²⁻¹⁵ In an assessment of the renal effects of dipyridamole and indomethacin in humans, researchers found that while both drugs have clear renal effects, combining them produced even more distinct reductions in renal function.¹⁶

Given this evidence, a dipyridamole-containing product such as Aggrenox® has the potential to reversibly reduce renal function under the correct pathophysiological circumstances.¹⁰ Adverse effects commonly associated with Aggrenox® therapy include headache, dyspepsia, abdominal pain, nausea and diarrhea. To our knowledge, the potential adverse effects on renal function have never directly been evaluated. We examined the adverse events reported to the Health Canada adverse reaction database related to Aggrenox® (up to 31 December 2007) and found three cases involving acute renal failure or increased serum creatinine. The only published case study we found describes a patient who suffered acute interstitial nephritis believed to be associated with Aggrenox®.¹⁷ An 83 year old man presented with nausea, vomiting and generalized weakness, four days after starting Aggrenox®. The patient had a normal serum creatinine (85 µmol/L) one year prior to this event. Creatinine was 494 µmol/L initially on admission and rose to 798 µmol/L on day 5 of admission. Aggrenox® and enalapril were held and IV normal saline was administered. Biopsy confirmed acute interstitial nephritis. It is not possible to completely exclude enalapril as the causal agent, but it is less likely since he had been on this medication for several years. By exclusion, Aggrenox® was the most likely cause of acute interstitial nephritis.¹⁷

Our objective was to try to determine if Aggrenox® was associated with the acute renal failure observed in three patients and to determine whether it was the ASA, dipyridamole or a combination of both that led to acute renal failure.

METHODS

Our hospital delivers complex continuing care and rehabilitation services with a bed capacity of 224. The special rehabilitation unit, where the acute renal failure occurred, provides services to patients who have experienced a stroke. Following diagnosis of a CVA at the acute care hospital in our community, the patients under discussion were started on Aggrenox®. Given that our unit works in collaboration with the acute care hospital, once these patients were medically stable they were transferred to our special rehabilitation unit. Over the course of three years, we experienced three cases of acute renal failure which appeared to be associated with Aggrenox® therapy. Patients began taking Aggrenox®, without any prior history of renal dysfunction, and presented with nausea, vomiting, diarrhea and generally felt unwell. All three patients were eventually found to be in acute renal failure.

Serum creatinine and Blood Urea Nitrogen (BUN) were measured to evaluate kidney function. Acute renal failure (ARF) occurs when renal function declines abruptly and can be detected by an increase in serum creatinine or urea.¹⁸⁻²⁰ More specifically, ARF was defined as an increase in serum creatinine of 44.2 µmol/L if baseline is less than 221 µmol/L or an increase of 20% if baseline is more than 221 µmol/L.²¹⁻²³ ARF is divided into three categories; prerenal, intrinsic and postrenal.^{18,19,24} The cases that we described were most consistent with prerenal ARF.

RESULTS

Patient 1 was admitted to the special rehabilitation unit following a right basal ganglia infarct. Significant medical history included dyslipidemia, hypertension, carotid endarterectomy, and prostatectomy. Significant medical history for Patient 2, included left hemispheric CVA, hypertension, osteoarthritis, dyslipidemia, type 2 diabetes and obesity. The third patient had a medical history of CVA, hypertension, dyslipidemia, chronic atrial fibrillation and esophageal stricture. None of these individuals were taking medication that would be nephrotoxic in someone with normal renal function (*see* Table 1 for a complete list of medications).

TABLE 1 Medications

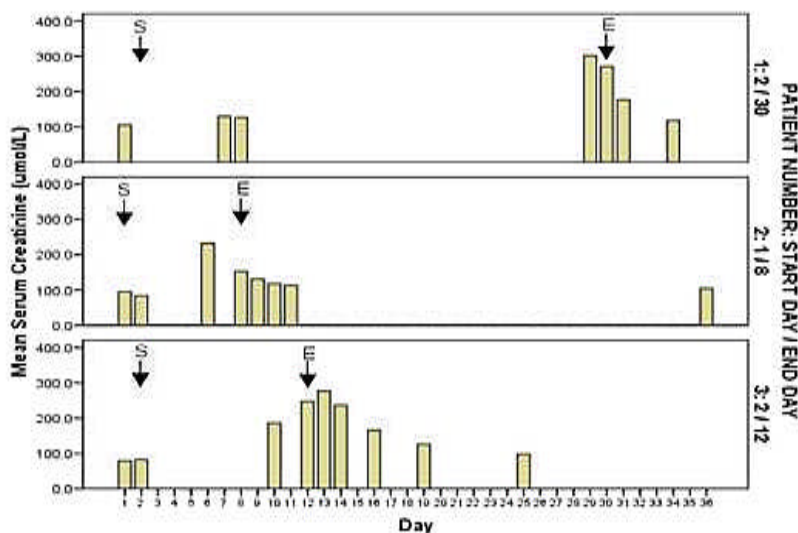
PATIENT 1		PATIENT 2		PATIENT 3	
Scheduled Medication	Therapy Course	Scheduled Medication	Therapy Course	Scheduled Medication	Therapy Course
Hydrochlorothiazide 25mg po bid	Day 2 to day 8	Dipyridamole/ASA	Day 1 to day 8	Docusate Sodium 100mg po od	Day 2 to day 25
Metoprolol 25mg po bid	Day 2 to day 8	Enoxaparin 40mg s/c daily	Day 1 to day 10	Losartan 100mg po od	Day 2 to day 21
Dipyridamole/ASA po bid	Day 2 to day 30	Triamterene/hctz 1 tab po od	Day 2 to day 11	Digoxin 0.125mg po od	Day 2 to day 11
Heparin 5000U s/c q 12 h	Day 2 to day 29	Domperidone 10mg tid & hs	Day 6 to day 38	Dyazide 50mg/25mg po od	Day 2 to day 27
2/3 – 1/3 + 20mEqKCl @ 100cc/hr	Day 30 to day 34	Normal saline IV	Day 6 to day 10	Dipyridamole/ASA po bid	Day 2 to day 12
Amlodipine 5mg po od	Day 2 to past day 36	Lansoprazole 30mg po od	Day 6 to day 11	Rosuvastatin 20mg po od	Day 8 to past day 25
Rosuvastatin 10mg po od	Day 2 to past day 36	Rabeprazole 20mg po od	Day 11 to day 38	ASA 81mg po od	Day 12 to past day 25
Salmeterol 2 puffs q 12 h	Day 2 to past day 36	Atorvastatin 80mg po od	Day 1 to past day 37	Digoxin 0.125mg po q2d	Day 14 to day 29
Omeprazole 20mg po bid	Day 7 to past day 36	Ramipril 5mg po od	Day 1 to past day 37	Losartan 50mg po od	Day 21 to day 25
Fluticasone 2 puffs q 12 h	Day 9 to past day 36	Docusate Sodium 100mg po od	Day 1 to past day 37		
Fluticasone 1 spray each nostril bid	Day 15 to past day 36	Celecoxib 100mg po od	Day 2 to past day 37	As Needed Medication	
Clopidogrel 75mg po od	Day 30 to past day 36	ASA 81mg po od	Day 9 to past day 37	Nitrospray prn	
		Cyanocobalamin 1000 µg	Day 9	Trazodone 25mg po hs pr	
		Triamterene/hctz 0.5 po od	Day 11 to past day 37	Acetaminophen 1-2 po q 4h prn	
				Acetaminophen 650mg pr q 4h prn	
As Needed Medication		As Needed Medication			
Sennosides 17.2mg po prn		Dimenhydrinate 25-50mg po q6h prn			
Meclizine 25mg po tid prn		Acetaminophen 1-2 po q 4h prn			
Ibuprofen 1-2 tabs qid prn		Laxative prn			
Fleet enema prn		Fleet prn			
Lactulose 15mL hs prn		Oxazepam 15mg hs prn			
Docusate Sodium 100mg po bid prn					
Zopiclone 7.5mg hs prn					
Bisacodyl 10mg pr q3d prn					
Acetaminophen 1-2 po q 4-6 h prn					
Hydrocortisone/clotrimazole bid prn					
Desonide cream bid prn					
Betamethasone dipropionate prn					
Salbutamol 1-2 puffs prn					

Therapy course is recorded in days, not dates, to avoid revealing potential identifiers of the described patients. The day numbers correlate with the day numbers used on the graphs for serum creatinine measurement. asa- acetylsalicylic acid; pr- rectally; bid- twice daily; po- orally; d- day; prn- as needed; hs- at bedtime; qid- four times daily; h- hour;q- every; hctz hydrochlorothiazide; s/c- subcutaneous; IV- intravenous; tid- three times daily; KCL- potassium chloride; od- daily.

For Patient 1, there were repeated reports of emesis and poor appetite, nausea, anorexia and diarrhea, all of which disappeared shortly after the discontinuation of Aggrenox® therapy. Patient 1 had a baseline serum creatinine of 105.4 µmol/L which rose to 301.6 µmol/L during therapy with Aggrenox®, representing an increase of 186%. Serum creatinine returned to baseline within 10

days of discontinuing Aggrenox® (see Figure 1). The highest creatinine level was measured at 301.6 µmol/L on day 29. Intra venous 2/3-1/3 @100 mL/hr was started the same day and by the next morning, the creatinine had decreased to 271.2 µmol/L.

Figure 1: Changes in renal function associated with Aggrenox therapy



Similarly, Patient 2 became very nauseated and unwell during Aggrenox® therapy, with multiple episodes of emesis. Patient 2 had a baseline serum creatinine of 95.5 µmol/L when Aggrenox® was initiated. This increased 144% to 233 µmol/L within six days of therapy, and returned to baseline within 10 days of discontinuing Aggrenox® (see Figure 1). Based on experience with the first case, the adverse effect of Aggrenox® in the second case was addressed more quickly, and the serum creatinine was monitored. Additionally, as soon as Aggrenox® was discontinued, ASA 81mg was started.

Shortly after Aggrenox® treatment was started, Patient 3 had episodes of nausea and vomiting. Patient 3 had a baseline serum creatinine of 79.5 µmol/L which rose to 277.4 µmol/L during Aggrenox® therapy, and then returned to baseline within 10 days of discontinuing Aggrenox®. This increase of 249%

was the largest change in serum creatinine that we observed (see Figure 1). These results are consistent with the other cases; the serum creatinine rose during therapy and returned to baseline on discontinuation of Aggrenox®. As with Patient 2, after the Aggrenox® was discontinued, ASA 81mg was started.

In three additional cases occurring in the same three year time period, patients presented similarly and improved on discontinuation of Aggrenox®. Suspected acute renal failure could not be confirmed retrospectively as creatinine and Blood Urea Nitrogen were either not reported or were insufficiently reported. In one of these cases, the patient already had chronic renal failure but showed signs (significant increase in serum creatinine and nausea) of acute on chronic renal failure during therapy with Aggrenox®. As a result, the data from these three additional cases were not included in this report.

DISCUSSION

These data support the theory that continued Aggrenox® therapy in some patients, leads to rising serum creatinine. In all cases, immediately after Aggrenox® was stopped, the serum creatinine began to decline to baseline, an observation that shows that the effect on kidney function is reversible in a short time. The reversibility of the reaction is most consistent with prerenal azotemia. Prerenal ARF is the most common type of ARF and is caused by a reduction in renal blood flow or impaired renal perfusion.^{18,19,24} Aggrenox®, as we have indicated, causes an increase in adenosine, which in turn reduces the GFR and renal perfusion. While this reaction appears to be fully reversible in a short period of time, if the reduction in renal blood flow is severe or prolonged, ischemic damage to the tubules may occur, resulting in acute tubular necrosis.^{18,20} In mild to moderate prerenal conditions, GFR and renal perfusion are maintained by autoregulatory mechanisms and BUN and serum creatinine remain normal.¹⁸ The autoregulatory mechanisms in the kidney that increase the hydrostatic pressure at the glomerulus in response to reduced renal perfusion were insufficient to overcome this situation.¹⁸

It must be considered that the most common cause of prerenal ARF is dehydration.²⁰ We did not feel that dehydration was the cause in these cases but rather contributed to worsening the situation. The episodes of nausea were significant, but emesis and diarrhea were far less frequent. In our clinical opinion, the fluid losses from emesis and diarrhea did not approach a level that would account for ARF in these patients. Also, the timing of events was not consistent with dehydration leading to renal failure.

Patient 1 appears to have shown a possible improvement in serum creatinine prior to the last dose of Aggrenox®. Such an anomaly could be explained by the increased sodium load from initiating IV sodium chloride/dextrose. Studies have shown that sodium load correlates to the renal effects that we see in the presence of increased adenosine. The renal vasoconstriction caused by adenosine is enhanced by maintaining animals on a low sodium diet.^{9,14} A low sodium diet acts to increase the activity of the renin-angiotensin system. The resultant afferent

arteriolar vasoconstriction is mediated by the effect of the increased adenosine on the intrarenal angiotensin system.⁹ Further study has revealed that inhibition of angiotensin II formation by feeding a high sodium diet blunts the renal vasoconstriction normally seen with adenosine infusions.^{8,10} In Patient 1, it is possible that the sodium influx from the IV solution affected the renin-angiotensin system such that the effect of increased adenosine on the afferent arteriole was somewhat blunted. Another explanation for the lower serum creatinine following intravenous infusion is that correcting volume depletion will improve renal perfusion and GFR in patients with prerenal azotemia.^{20,24,25}

In the second case, which involved Patient 2, the graph shows a distinct rise in serum creatinine during Aggrenox® therapy. There was one day where serum creatinine was not drawn which may have clarified what specifically occurred with renal function on day 7. The highest measured creatinine level was 233 µmol/L on day 6. The last dose of Aggrenox® was administered on day 8. When the creatinine was at the highest measured level of 233 µmol/L, IV normal saline 100mL/hr was started that afternoon. It is possible that serum creatinine may have started to fall before the last dose of Aggrenox® since IV normal saline was started. The influx of sodium may have reduced the activity of the renin-angiotensin system, thereby blunting the effect of increased adenosine. Alternatively, the normal saline infusion would correct hypovolemia resulting in improved renal blood flow and account for a lower serum creatinine.^{20,24,25}

When we examined the adverse events reported to the Health Canada's adverse drug reaction (ADR) database related to Aggrenox®, there were several cases reporting nausea and vomiting. Since our cases of acute renal failure also presented with nausea and vomiting, it is possible that some of the reported cases of nausea and vomiting suffered changes in renal function that went undetected.

CONCLUSION

There is substantial information in the literature linking dipyridamole to a reduction in GFR.^{6,8,10-17,26,27} Hence, it is biologically plausible that dipyridamole may contribute to renal dysfunction

in some individuals. While the evidence presented here is by no means conclusive, it is noteworthy, and points to a need for further examination of the impact of Aggrenox® therapy on renal function. Perhaps assessment of renal function should be a monitoring parameter with Aggrenox® therapy, as it may prove beneficial to patients, especially those experiencing nausea or vomiting after starting therapy.

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