Case Report

Co-Trimoxazole Induced Multi-Organ Failure

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INTRODUCTION

The sulfonamide antibiotics are amongst the oldest antimicrobials in current use with widespread application since their introduction in 1936.[1] Extensive clinical experience has demonstrated that the sulfonamide antibiotics can cause a wide variety of adverse reactions. The most common being cutaneous reactions, typically exanthematous or urticarial rashes, which occur in up to 5% of patients.[2] Less commonly, sulfonamides can cause idiosyncratic or hypersensitivity adverse drug reactions potentially involving 1 or more different organs. Liver, kidney, blood, thyroid, and cardiac toxicities have been attributed to the sulfonamides.[3-7] The incidence of sulfonamide hypersensitivity reactions is extremely low: 1 in 1,000 to 10,000 patients treated.[2]

The following case illustrates a patient who developed a hypersensitivity reaction to co-trimoxazole (trimethoprim-sulfamethoxazole) involving cutaneous, hepatic, hematologic, and renal toxicities. The case exemplifies the acute nature and potential severity of such multi-organ reactions. Given the current widespread use of sulfonamides, clinicians should be aware of how these reactions present and progress, to ensure their prompt recognition and appropriate management.

CASE

GH, a 47 year-old Caucasian woman, was prescribed a 10-day course of co-trimoxazole for symptoms of frequency, urgency, and dysuria. On the ninth day of therapy, she developed an itchy skin rash, and began experiencing episodes of fever, frontal headaches, decreased appetite, nausea, vomiting, diarrhea, and generalized weakness. For her myalgias and discomfort, she took ibuprofen on an intermittent basis with minimal relief. The next day she presented to the Emergency Department with persistent symptoms as described above. As part of her medical work up, blood work was done; she was given acetaminophen for symptomatic treatment and discharged without a clear provisional diagnosis.

She was called back into the Emergency Department the next day upon notice of her abnormal blood work (Table I). She had developed a generalized maculopapular erythematous pruritic rash, and a drug-induced allergic-type hepatitis was suspected to account for her symptoms. Special coagulation parameters tested

Table I. Summary of Significant Laboratory Findings Throughout Patient's Hospital Stay.

TEST (normal range of values)	Initial presentation (Day -1)	ER visit (Day 0)	Day 2	Day 3	Day 5	Day 10	Day 14
AST (U/L) (< 40)	6310	> 60000	8279	3366	599	51	54
ALT (U/L) (7-56)	6006	14355	8439	5094	2875	266	170
LDH (U/L) (300-550)	30567	68199	31582	7368			
Alk.Phos (U/L) (35-105)	217	205	159	169	194	219	207
Total bilirubin (µmol/L) (<20)	42	80	80	108	106	161	129
albumin (g/L) (35-48)		32				27	26
INR (0.9-1.1)	1.8	1.8	2.2	2.5	1.5	1.3	1.1
aPTT (s) (25-34)	32.7	44.8	57.9	61	40.8	31.8	30.6
WBC (G/L) (4-11)	2.9	7.4	5.3	4.5	6.3	11.7	8
eosinophils (G/L) (<0.4)	0	0.1	0.7		0.8		0.1
SCr (umol/L) (40-120)	103	437	561	609	996	584	427
BUN (mmol/L) (2.5-8.0)	4.2	13.5	17.1	14.5	24	11.8	11.5

ER= emergency department, AST= aspartate transaminase, ALT = alanine transaminase, LDH = lactic dehydrogenase, Alk.Phos= alkaline phosphatase, INR = international normalized ratio, aPTT = activated partial thromboplastin time, WBC = white blood cell count, SCr= serum creatinine, BUN = blood urea nitrogen

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included a fibrin degradation product concentration of 80 mg/L and a normal fibrinogen concentration. Urinalysis was normal. Further evaluations included an acetaminophen level of 103 µmol/L and a salicylate level of 0.47 mmol/L (supratherapeutic levels at our institution are > 250 µmol/L at 12 hours and >2.20 mmol/L, respectively). On physical examination, she had a diffuse rash covering most of her body and limbs. She was alert, oriented, and afebrile. She had a soft abdomen with mild right upper quadrant tenderness, and splenomegaly. Her previous medical history included a motor vehicle accident in 1976 and a diagnosis of hypothyroidism, for which she was receiving levothyroxine 0.1 mg daily. She had no history of hepatitis and had never had an allergic reaction to any drug. She was on no other medications, she did not smoke nor abuse alcohol. The patient was admitted to the Intensive Care Unit for further evaluation and supportive care.

By day 2 of her admission, the high liver transaminase concentrations began to decrease. However, her renal function continued to deteriorate and continuous arteriovenous hemodialysis (CAVHD) was initiated. A hepatorenal syndrome was ruled out with a urine sodium concentration of 35 mmol/L. At this time, there was shortness of breath, and crackles from mid-lung down. A chest x-ray revealed diffuse bilateral pulmonary edema. The patient complained of nausea unrelieved by dimenhydrinate 25-50 mg PO/IV given every 4 hours, but controlled with prochlorperazine 10 mg IV every 6 hours. The skin rash remained pruritic. Diphenhydramine 25-50 mg PO/IV every 6 hours was given to minimize the itching.

Over the following 3 days, there was a dramatic decrease in the AST and ALT concentrations, but the BUN and serum creatinine continued to rise despite the use of CAVHD (Table I). Urine output was minimal. Symptomatically she reported feeling better, with no nausea or vomiting, was tolerating solid foods, and had only a mild itch. On day 7 of hospitalization, she was transferred to the renal ward and the CAVHD was replaced by intermittent hemodialysis on a 3-times per week basis. Over the following 2 days, her renal function continued to improve and there was a marked decrease in most liver enzyme concentrations.

On day 14, the patient was discharged back to her local hospital for continued intermittent hemodialysis. The rash had nearly resolved, and the final laboratory findings were as noted in Table I. Additional investigations included a negative blood culture and negative hepatitis serology. The patient's thyroid function was not assessed during her hospital stay; however, she continued to receive levothyroxine, and a recommendation was made to test the thyroid-stimulating hormone (TSH) a month after discharge from hospital. Further follow-up has not been possible, as the patient returned to the United States.

DISCUSSION

Similar to a number of drugs including isoniazid, hydralazine, and procainamide, the major pathway of sulfonamide metabolism involves acetylation of the aromatic amine portion of the molecule by N-acetyl-transferase (NAT).[2,4,8] This metabolic pathway results in a non-toxic metabolite. An alternative oxidative pathway, via the cytochrome P_{450} mixed-function oxidase system, appears to be responsible for the transformation of the parent molecule into hydroxylamines, which are reactive molecules capable of covalently binding to cell macromolecules and causing cellular damage.[4,6] It is not known which specific P_{450} isoenzymes are responsible for generating these reactive molecules.[1] The availability of detoxification pathways for the hydroxylamine allows for the conversion of these substances into non-toxic metabolites.[4] The detoxification pathway involves, in part, conjugation with glutathione.[1]

The NAT enzyme exhibits polymorphic activity for a variety of compounds including sulfonamides. This accounts for the existence of "slow" and "fast" acetylator phenotypes, based on the quantity of enzyme available.[2] It has been speculated that slow acetylators (approximately 50% of Caucasians and blacks) would be at increased risk for the development of hypersensitivity reactions to sulfonamides due to a larger portion of the parent drug undergoing oxidation via the cytochrome P_{450} system.[2,9] However, since the incidence of these hypersensitivity reactions is not 50% but less than 1%, there must be some other process involved which determines an individual's susceptibility to these reactions. Thus, pharmacogenetic differences between individuals in their detoxification capacity for the hydroxylamine metabolites may be responsible.[4]

The type, severity, and sequence of organs typically involved in sulfonamide hypersensitivity reactions may depend on the availability of each of the metabolic pathways in the different organs.[4] Immunological responses to cell-specific cytotoxicity may be responsible for the variations in clinical presentation among patients.[4]

There is a characteristic sequential order of organ involvement in the clinical course of hypersensitivity reactions secondary to sulfonamides.[4] Typically, symptoms begin with a sudden onset of high fever 10 to 14 days after the initial exposure to the drug. The development of a skin rash, which varies from morbilliform rashes to erythema multiforme including Stevens-Johnson syndrome or toxic epidermal necrolysis, follows within hours.[2,4] Organ involvement such as hepatitis, renal failure, cardiac toxicity, hematological abnormalities, and

neural toxicity alone or in combination, accompany these reactions within days to weeks.[2,4] A late complication of these reactions is hypothyroidism, which appears to occur 1 or 2 months after initial exposure to the sulfonamide and persist for as long as 2 years.[6] The mechanism underlying thyroid involvement appears related to the capacity of thyroid peroxidases to produce the hydroxylamine metabolites.[6]

Many features of the case described above are consistent with a sulfonamide-induced hypersensitivity reaction. Firstly, the time sequence of events matches what has been described in the literature: the onset of the maculopapular pruritic rash within 9 days of initial exposure to co-trimoxazole, followed by the involvement of the liver, blood, and kidneys. Secondly, the characteristics of the patient's hepatic involvement are consistent with what has been described as sulfonamide-induced liver injury: the presence of eosinophilia, high concentrations of transaminases, a sharp rise in the serum concentration of alkaline phosphatase (attaining high concentrations relatively early in the disease), and an increase in serum bilirubin.[10,11] According to previous reports, and consistent with this patient, these reactions may run a fulminant course despite the absence of further exposure to the drug. Thirdly, the characteristics of renal failure in this patient have similarities with the renal damage that has been reported to occur with sulfonamides. It appears that typically, patients have a microscopic or gross hematuria/crystalluria (not observed in this patient) and oliguric or anuric renal failure.[12] It has been suggested that sulfonamides can cause 1 of 4 types of injury to the kidney: vasculitis, glomerulonephritis, acute interstitial nephritis (AIN), or acute tubular necrosis (ATN).[12-14]

Upon presentation, diagnoses other than that of a drug-induced hypersensitivity reaction were considered in this patient. Since she had originally come from the North-Eastern United States, where Lyme Disease is prevalent, this disorder was suggested as a possible etiology.[15] However, although she did present with a non-specific diffuse rash, there was no history of exposure to ticks, nor any neurological involvement suggestive of Lyme Disease.[16] Other possible diagnoses considered were Epstein-Barr virus and infectious hepatitis. The former was ruled out due to the absence of the typical symptoms of infectious mononucleosis such as lymphadenopathy and pharingitis. Infectious hepatitis was ruled out based on serology.

Although the patient's clinical features seemed consistent with a sulfonamide-induced hypersensitivity reaction, a particular discrepancy deserves mention. Upon admission, the patient was afebrile, although the ibuprofen and acetaminophen she had been taking prior to admission may have masked a febrile response to her illness.

It is possible to determine whether an individual is a slow or fast acetylator by means of acetylator phenotyping. This test involves the administration of caffeine (which has been shown to be metabolized by the NAT) and measuring of the ratio of parent compound to metabolite excreted in the urine.[1,8] Furthermore, it is possible to determine an individual's ability to detoxify the hydroxylamines using the lymphocyte cytotoxicity assay, originally described by Spielberg.[17] In this assay, lymphocytes act as a tissue on which to evaluate sulfonamide-induced cytotoxicity via measurement of cell death.

At our institution, the acetylator phenotyping and the lymphocyte cytotoxicity assay are not available. Had these tests been performed, it may have been possible to confirm whether this was truly a hypersensitivity reaction to co-trimoxazole. However, given the delay in the onset of symptoms, the characteristic sequence of events, and the multi-system involvement, a sulfonamide-induced hypersensitivity reaction seems the most likely explanation for this patient's presentation and clinical course.

Trimethoprim, as a component of co-trimoxazole, is unlikely to have been the causative agent of the hypersensitivity reaction mainly for 2 reasons. Firstly, toxicity with trimethoprim is low. Although nausea, vomiting and malaise may occur, the development of cutaneous or hematologic toxicities is rare, with most cases occurring when used in combination with a sulfonamide.[18,19] Secondly, a literature search revealed no reports of hypersensitivity reaction due to trimethoprim, whereas various sulfonamide preparations including sulfadiazine, sulfamethazine, and sulfamerazine have been associated with idiosyncratic toxicities.[1]

The potential of acetaminophen to cause hepatic toxicity is well known. Acetaminophen was ruled out as a contributing or causative agent in producing our patient's hepatic toxicity given the short term and low doses used and the non-toxic serum levels obtained.

The multi-organ toxicity following sulfonamide hypersensitivity reaction can be expected to resolve over days to weeks upon withdrawal of the drug.[4] However, hypothyroidism can occur as a late complication. Interestingly, this patient had underlying hypothyroidism for which she was receiving thyroid replacement therapy. Whether the hypothyroidism is likely to worsen in this patient months after the acute incident is unknown. Thus, upon discharge from the hospital, the patient was advised to have her TSH level measured 1 or 2 months later. She was also advised to avoid co-trimoxazole and any other sulfonamide drugs in the future, as previous literature reports suggest that therapeutic rechallenge with the offending sulfonamide would be expected to cause similar and perhaps worse disease.[4]

Although case-control studies of a particular idiosyncratic reaction secondary to sulfonamides such as hepatitis have been published, a Medline search revealed only 1 detailed case report of the multi-organ phenomenon.[4] The patient, a previously healthy 13 year-old black male who was prescribed co-trimoxazole exhibited a sequential clinical course similar to that of our patient, beginning with a rash and fever, and progressing to hepatic, renal, and hematologic toxicity. Contrary to our patient, however, cardiac toxicity was observed in that case. Although a gradual resolution of all adverse effects was seen, the boy was noted to be hypothyroid 2 months after the onset of the illness.

In conclusion, many features of our case lead us to the diagnosis of a sulfonamide-induced hypersensitivity reaction and to the exclusion of other possible diagnoses. However, it was a difficult diagnosis to establish with absolute certainty since sophisticated biochemical laboratory procedures such as acetylator phenotyping and the lymphocyte cytotoxicity assay are not currently offered as clinical diagnostic tools.

This case demonstrates the potential acuity and severity of a sulfonamide hypersensitivity reaction involving both the liver and the kidneys. It is important for clinicians to recognize the features of a sulfonamide hypersensitivity reaction early in its clinical course, in order to discontinue the drug and minimize potentially serious sequelae. The difficulty lies in distinguishing a common allergic reaction such as a rash from this rare but potentially multi-system phenomenon which also typically presents as a rash.

A high level of suspicion is often all that there is to rely upon for the presence of drug-induced reactions. Sulfonamide-induced hypersensitivity reactions should be considered in the differential diagnosis of any patient receiving a sulfonamide who presents with fever, rash, and 1 or more organ toxicity of no other obvious cause.

However, the rare incidence of these reactions must be considered. There is not a need for suspecting such reactions in every 1 of the thousands of patients seen on a daily basis who are receiving sulfonamides. It is important to remember that the therapeutic benefits drawn from these drugs far outweigh any risks of these rare, but serious idiosyncratic reactions.

The small number of individual reports currently in the literature which describe this phenomenon makes it difficult to collate and interpret the data. However, the continued reporting of cases of such rare occurrence would increase the quantity and quality of data collected and may result in a better understanding of sulfonamide-induced hypersensitivity reactions.

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