Observational Study

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Observational study of the clinical utility of sulfamethoxazole serum level monitoring in the treatment of brain abscesses due to *Nocardia* species

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Abstract

Although there is a lack of data in trimethoprim-sulfamethoxazole (TMP-SMX) serum monitoring utility for invasive nocardial infections, therapeutic drug monitoring is widely used to optimize dosing and avoid adverse reactions that may cause treatment interruption.

We retrospectively reviewed all adults who received TMP-SMX to treat nocardial brain abscess and had SMX serum level testing from 2010 to 2020.

Twenty-two patients received treatment with TMP-SMX for *Nocardia* species brain abscess and 16 (72.7%) had a reported SMX level, with a median patient age of 65.5 years (interquartile range, IQR 59.5–72.5). Compared to those who did not have a documented SMX serum level, patients with SMX levels had a shorter median course of TMP-SMX treatment (322 days [IQR 188–365] vs. 365 [IQR 224–365]; $P = .31$) and higher therapeutic induction dose (10 [62.5%] vs. 3 [50%]; $P = .92$). Similarly, they were more frequently on hemodialysis (3 [13.6%] vs. 1 [4.5%]; $P = > .99$). The median peak level was 158.5 (IQR 120–218) μg/mL, collected at 2 hours (75%) post-administration in the induction phase (81.3%). Patients with documented SMX levels had fewer reported drug toxicity (5 [31.3%] vs. 4 [66.7%]; $P = .1$) than those without SMX levels. Among the five patients who reported TMP-SMX-related toxicity, 4 (80%) had an SMX peak level >150 μg/mL. There was no difference in the cure, relapse, and death rates among the two groups.

While SMX level was not associated with *Nocardia* species brain abscess cure rates and mortality, most patients with SMX peak >150 μg/mL experienced drug toxicity.

Abbreviations: AKI = acute kidney injury, IQR = interquartile range, spp. = species, TMP-SMX = trimethoprim-sulfamethoxazole.

Keywords: brain abscess, nocardia, outcomes, serum level, sulfamethoxazole

1. Introduction

Despite the introduction of newer antibiotics, diagnostics, and therapeutic procedures, the mortality rates for nocardial brain abscesses remain high, up to 30%, compared to 10% for other bacterial causes.[1,2] The treatment choice remains challenging, as there are no randomized clinical trials to compare the efficacy of different antibiotic regimens for nocardiosis; however, the well-known active agents against *Nocardia* species (spp.) are trimethoprim-sulfamethoxazole (TMP-SMX), amikacin, minocycline, and imipenem.[3] Sulfonamides and trimethoprim are small lipophilic antibiotics. At high doses (5 mg of TMP and 25 mg of SMX per kg of body weight), the penetration into the cerebrospinal fluid is considered sufficient for treating central nervous system infections.[4,5] Currently, TMP-SMX is viewed as the mainstay of therapy in susceptible isolates.[6]

Since TMP-SMX has consistently demonstrated significant interindividual pharmacokinetics variability, therapeutic drug monitoring is often used to optimize dosing and avoid adverse reactions that may contribute to treatment interruption.[7] While data exists on the use of SMX level monitoring for *Pneumocystis jirovecii* pneumonia,[8] there is a lack of data in SMX serum monitoring utility for invasive nocardial infections. Therefore, we aimed to describe the clinical utility of SMX serum level monitoring in treating brain abscesses due to *Nocardia* spp. in a contemporary cohort at a large referral center.

2. Materials and methods

We retrospectively reviewed all adult (≥18 years of age) patients who received TMP-SMX to treat nocardial brain abscess and

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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underwent SMX testing levels from January 1, 2009 through June 30, 2020. Patients' electronic health records were reviewed. All the patients had consented to use their medical records for research purposes, and the study was approved by the Mayo Clinic Institutional Review Board (IRB# 21-001470).

A search was conducted using an Advanced Cohort Explorer tool developed by Mayo Clinic using "brain abscess." Case definitions, microbiologic information, and variables included in this database have been described in earlier publications.[9] Polymicrobial infections were excluded.

The SMX peak was defined as the level obtained 1 hour after the intravenous dose, or 2 to 3 hours after an oral dose. A peak of 100 to 150 μg/mL has been suggested as the target for SMX levels in nocardial infections.[10] Higher TMP-SMX therapeutic dose was defined as two double strength tablets twice or three times a day; whereas a lower therapeutic dose was defined as one double strength tablet twice a day or three times a day. Oral double-strength tablet dosage was 160 mg TMP/800 mg SMX and, intravenous dosage was 80 mg TMP/400 mg SMX per 5 mL. Laboratory assessment SMX serum concentration levels were determined by liquid-chromatography mass spectrometry by our institution's Clinic Toxicology and Drug Monitoring Laboratory.[11] Failure was defined as a relapse, brain abscess size progression, or the development of a new abscess with the same bacterial etiology within 3 months despite initial medical or surgical therapy. Acute kidney injury (AKI) for patients who did not have chronic kidney disease was defined as an increase in the serum creatinine concentration of ≥0.3 mg/dL from baseline, a percentage increase in the serum creatinine concentration of ≥50% or oliguria. For patients with chronic kidney disease, AKI was defined as an increase in serum creatinine of ≥50%.[12] Of note, the patients with an initially normal renal function also needed to have an increase in Blood Urea Nitrogen of 10 mg/dL.[13,14]

2.1. Statistical analysis

Descriptive information about patients with brain abscesses was reported as frequencies and percentages for categorical variables or median (interquartile range [IQR]) for continuous variables. Statistical tests were 2-tailed, with $P < .05$ considered statistically significant. Statistical analysis was performed using BlueSky Statistics software v7.2 (BlueSky Statistics LLC, Chicago, IL).

3. Results

3.1. Demographic and radiologic characteristics

Comparisons of demographic, comorbidities, and radiographic characteristics of patients with *Nocardia* spp. brain abscess with and without SMX levels are summarized in Table 1. Overall, 24 patients were diagnosed with *Nocardia* spp. brain abscess. Of them, 22 (91.7%) were treated with TMP-SMX, and 16 (72.7%) had a documented SMX level. Medical comorbidities were similar for both groups, including diabetes mellitus, chronic kidney disease, and vascular disease. Compared to those who did not have a documented SMX serum level, there was a higher percentage of patient with hemodialysis in the SMX levels group (hemodialysis, 3 [13.6%] vs. 1 [4.5%]); however, this difference was not statistically significant. None of 22 patients had a preexisting central nervous system hardware.

At the time of admission, no statistically significant differences were observed in the radiologic characteristics that included the

Table 1

Demographic, comorbidities, and radiographic characteristics of patients with *Nocardia* species brain abscess with and without SMX levels.

	No SMX levels (n = 6)	SMX levels (n = 16)	Total (n = 22)	$P^{*,\dagger}$
Age median (IQR), y	61.5 (50–64)	65.5 (59.5–72.5)	64 (58–69)	.16
Male, n (%)	3 (50)	14 (87.5)	17 (77.3)	.10
White Race, n (%)	5 (83.3)	15 (93.8)	20 (90.9)	.48
Prior head/neck surgery, n (%)	0 (0)	2 (12.5)	2 (9.1)	>.99
Comorbidities, n (%)				.65
Diabetes mellitus	3 (50)	4 (25)	7 (31.8)	
Malignancy	2 (33.3)	8 (50)	10 (45.5)	
History of stroke	0 (0)	1 (6.3)	1 (4.5)	
Immunosuppressive therapy	4 (66.7)	9 (56.3)	13 (59.1)	
Bone marrow transplant	2 (33.3)	1 (6.3)	3 (13.6)	
Solid organ transplant	3 (50)	4 (25)	7 (31.8)	
Hypertension	2 (33.3)	5 (31.3)	7 (31.8)	
Chronic kidney disease	3 (50)	7 (43.8)	10 (45.5)	
Hemodialysis	1 (4.5)	3 (13.6)	4 (18.2)	>.99
CCI, median (IQR)	6 (4–9)	7 (5–10)	7 (5–10)	.74
Brain abscess location, n (%)				
Frontal lobe	2 (33.3)	7 (43.8)	9 (40.9)	>.99
Temporal lobe	4 (66.7)	3 (18.8)	7 (31.8)	.05
Parietal lobe	2 (33.3)	6 (37.5)	8 (36.4)	>.99
Occipital lobe	2 (33.3)	1 (6.3)	3 (13.6)	.17
Cerebellum and brainstem	1 (16.7)	4 (25)	5 (22.7)	>.99
Fluid collection size, median, cm (IQR)	1.8 (1–2.1)	1.3 (0.9–2.15)	1.5 (1–2.1)	.58
Midline shift, n (%)	1 (16.7)	1 (6.3)	2 (9.1)	.48
Single fluid collection, n (%)	3 (50)	11 (68.8)	14 (63.6)	.62

CCI = Charlson Comorbidity Index, IQR = interquartile range, n = number, SMX = sulfamethoxazole, y = years.

* Fisher's test.

† Mann–Whitney *U* test.

presence of brain midline shift (6.3% vs. 16.7%; $P=.48$), the median size of the fluid collection (1.3 cm [IQR 0.9–2.1] vs. 1.8 cm [IQR 1–2.1]; $P=.58$) and the presence of a single fluid collection (68.8% vs. 50%; $P=.62$).

3.2. Management

A total of 10 (45.5%) patients had a therapeutic surgical intervention (7 [43.7%] in those with SMX levels, vs. 3 [50%] without SMX levels; $P\geq.99$). There was no difference in the overall median time from brain abscess diagnosis to surgical management, which was 5 days (IQR 0–73) and 7 days (IQR 1–9) in each group, respectively. All patients had an infectious diseases consultation during their hospitalization.

Compared to those without a documented SMX serum level, patients with SMX levels had a shorter median course of treatment with TMP-SMX (322 days [IQR 188–365] vs. 365 days [IQR 224–365]; $P=.31$), and higher therapeutic dose (10 [62.5%] vs. 3 [50%]; $P=.92$), both statistically nonsignificant.

Individual characteristics of patients treated with TMP-SMX for *Nocardia* species brain abscess is summarized in Table 2. A total of 7 patients (32%) received TMP-SMX monotherapy as their final antibiotic therapy. In patients where SMX levels were obtained, a total of 9 (56.3%) had a peak level >150 μg/mL. The median peak level was 158.5 (IQR 120–218) μg/mL, collected at 2 hours (75%) post-administration in the induction phase (81.3%). The most common recommendation (50%) was to continue therapy based on the first level results followed by decreased TMP-SMX dose (37.5%). Only one patient had an increased dose based on sulfa level result. For second sulfa level assessment, most frequent response was to decrease TMP-SMX dose (50%).

3.3. Outcomes

A total of 9 (41%) patients reported TMP-SMX-related toxicity. Compared to those who did not have a documented SMX serum level, a numerically lower (nonsignificant) percentage of patients with documented SMX levels had reported drug toxicities (5 [31.3%] vs. 4 [66.7%]; $P=.1$), and the most common included nausea (3 [60%] vs. 1 [25%]; $P=.5$), AKI (1 [20%] vs. 2 [50%]; $P=.5$), and thrombocytopenia (1 [20%] vs. 1 [25%]; $P\geq.99$), respectively. Among the five patients with documented SMX levels who reported TMP-SMX-related toxicity, 4 (80%) had a SMX peak level >150 μg/mL (AKI [n = 1], thrombocytopenia [n = 1], and nausea [n = 2]; Supplementary Table 1, http://links.lww.com/MD/G628). Of note, toxicity was not associated with mg/kg/day TMP dose.

A total of 14 (9 [56.3%] vs. 5 [83.3%]) patients were cured, 4 (3 [18.8%] vs. 1 [16.7%]) relapsed, and 2 (2 [12.5%] vs. 0 [0%]) died, when comparing groups with and without SMX levels, respectively ($P=.9$). The patients with death or relapse were more likely to be a higher mg/kg/day dose TMP than those who were cured ($P=.006$; Supplementary Table 2, http://links.lww.com/MD/G629).

4. Discussion

Our study is one of the largest contemporary cohort that highlights the clinical utility of SMX serum level monitoring in treating nocardial brain abscesses. While sulfonamides have been the antimicrobials of choice to treat nocardiosis for the past five decades,[15] adverse reactions to high-dose TMP-SMX therapy are frequent and often associated with treatment interruption.

The results of our study demonstrate that peak SMX concentrations exhibit high variability even despite weight-based dosing adjusted for renal function, whereby a higher proportion of patients in our cohort with hemodialysis had frequent (at least twice) monitoring of the peak level. The free SMX form is therapeutically active and excreted in urine as an unchanged drug. As a renally eliminated antimicrobial agent, subclinical changes in glomerular filtration rate and contemporary methods of renal replacement may substantially alter the plasma

Table 2

Individual characteristics of patients treated with trimethoprim/sulfamethoxazole for *Nocardia* species brain abscess.

	Trimethoprim/sulfamethoxazole										
Patient/HD (y)	Dose	Therapy	Route	Time*	SMX peak level 1†	Dosing modification	Time*	SMX peak level 2†	Dosing modification	Cure (y/n)	Toxicity (y/n)‡
1	1 DS TID	Induction	Oral	2	123	Continue				y	n
2/y	2 DS TID	Induction	Oral	2	276	Decrease	1	264	Decrease	n	y
3	2 DS TID	Maintenance	Oral	2	190	Decrease	2			n	n
4	2 DS BID	Induction	Oral	2	199	Decrease	2	157	Continue	y	y
5	1 DS TID	Maintenance	Oral	1	245	Decrease				n	y
6	1 DS BID	Induction	Oral	3	92	Continue	3	168	Decrease	y	n
7	2 DS TID	Induction	Oral	2	166	Continue				n	n
8/y	1 DS TID	Induction	IV	2	102	Continue	2	135	Continue	y	n
9	2 DS BID	Induction	Oral	2	120	Continue				y	n
10	1 DS BID	Induction	Oral	3	12	Increase				n	n
11	2 DS TID	Induction	Oral	2	226	Decrease	2	256	Decrease	y	y
12	2 DS BID	Induction	Oral	2	120	Continue				y	n
13/y	2 DS BID	Induction	IV	2	210	Hold	2	62	Increase	n	n
14	1 DS BID	Maintenance	Oral	3	282	Decrease				y	y
15	2 DS TID	Induction	Oral	2	151	Continue	2	173	Decrease	y	n
16	2 DS BID	Induction	Oral	2	145	Continue	2	159	Continue	n	n

BID = twice a day, DS = double strength, HD = hemodialysis, IV = intravenous, n = no, PO = oral, SMX = sulfamethoxazole, TID = three times a day, y = yes.

* Sampling: hours post-dosing administration

† μg/mL

‡ Toxicities included nausea, thrombocytopenia, and acute kidney injury.

concentrations of SMX. Hence, appropriate drug dosing and monitoring are recommended.[16]

In patients with *Pneumocystis jirovecii* pneumonia, Chin et al[17] and Blaser et al[18] demonstrated that divided doses of 25 to 50 mg/kg per day of the SMX component produce sulfonamide serum concentrations between 100 and 150 μg/mL. This observation has been extrapolated to drug efficacy regardless of the targeted organ disease. Although earlier studies have found that individual SMX level monitoring has no effect in limiting toxicity,[19,20] adverse events are a significant concern in patients that require high SMX doses in the setting of life-threatening diseases such as central nervous system infections, when higher and frequent doses are often recommended.[21] Klinker et al recommended monitoring SMX levels in patients with *Pneumocystis* pneumonia to reduce adverse effects based on their finding of increased toxicity from higher SMX (200 μg/mL) levels.[22] As seen in our cohort, the median SMX peak level was 158.5 μg/mL, and the majority (80%) of the patients with an SMX peak level >150 μg/mL had a documented TMP-SMX-related toxicity regardless of the prescribed dose. Higher serum SMX concentration associates with toxicity; hence, obtaining SMX level is helpful in this regard which is also concordant to previous clinical studies.[23] TMP-SMX therapy-related toxicity is frequent. They often include myelosuppression, hepatoxicity, and renal insufficiency.[24] Not obtaining drug levels and choosing reduced versus conventional standard doses of TMP-SMX to cause less toxicity is not supported by any evidence.

Even though no statistically significant differences in patients' curative or mortality outcomes between TMP-SMX doses and frequent SMX level monitoring have been reported,[8–10] more diligent drug monitoring in patients with higher and frequent dosages could counteract the aforementioned toxicity concerns.

The study's retrospective nature with a case determination based on the claim dataset is the primary limitation. Likely due to the small size of our cohort, we were unable to report statistically significant results; however, we provide hypothesis generating data and potentially valuable information on therapeutic drug monitoring for an uncommon disease state in clinical practice. Similarly, the peak SMX concentrations from both oral and intravenous administration were combined for analysis, which may lead to difficulties in interpretation. As observed in our study, the patients with higher mg/kg TMP doses were more likely to have worse outcomes; nevertheless, selection biases could have influenced the decision for higher therapeutic doses in sicker patients or those with severe disease.

5. Conclusion

Majority of patients with SMX peak >150 μg/mL experienced drug toxicity; hence, SMX peak level monitoring may be helpful for drug toxicity monitoring in patients with *Nocardia* spp. brain abscess.

Author contributions

Cristina Corsini Campioli: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Visualization; Roles/Writing – original draft; Writing – review & editing
Omar Abu Saleh: Writing – review & editing
Kristin C. Mara: Data curation
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