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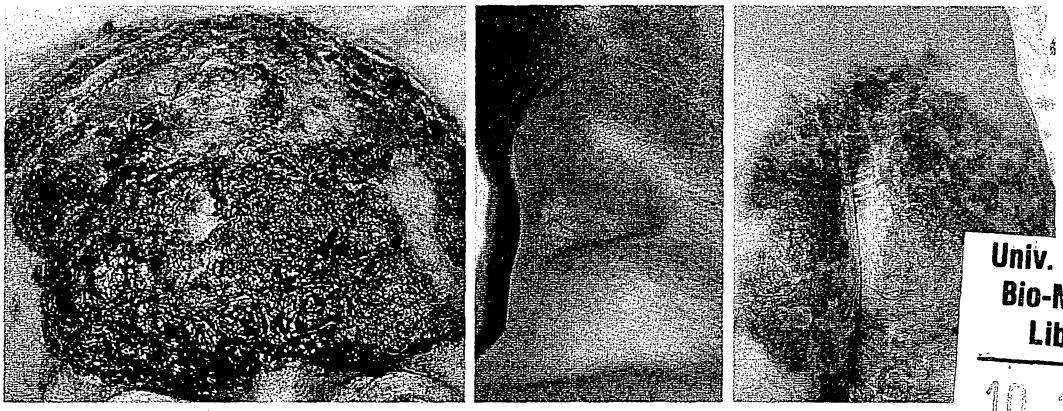
OCTOBER 1997



Question: What do these 3 individuals have in common? See page 1311.

THE AGING ISSUE

American Medical Association

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CURRENT AWARENESS ISSUE

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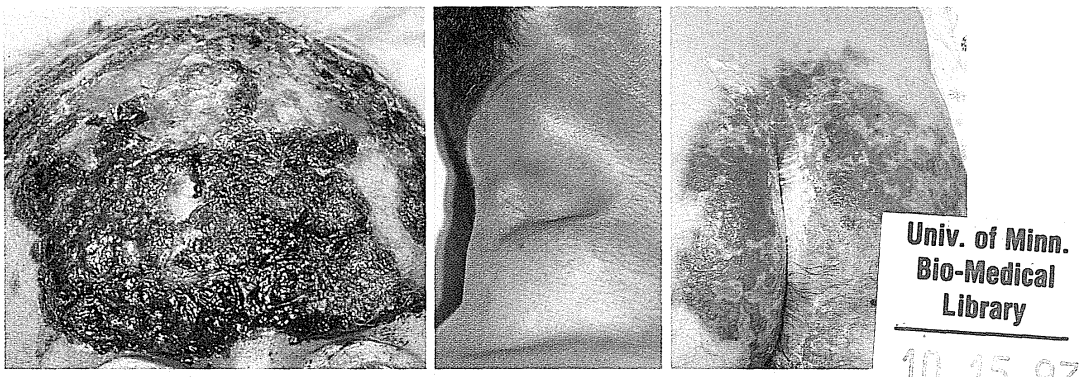

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THE AGING ISSUE

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STUDY

Comparative Safety of Tetracycline, Minocycline, and Doxycycline

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Background: Because minocycline can cause serious adverse events including hypersensitivity syndrome reaction (HSR), serum sicknesslike reaction (SSLR), and drug-induced lupus, a follow-up study based on a retrospective review of our Drug Safety Clinic and the Health Protection Branch databases and a literature review was conducted to determine if similar rare events are associated with tetracycline and doxycycline. Cases of isolated single organ dysfunction (SOD) attributable to the use of these antibiotics also were identified.

Observations: Nineteen cases of HSR due to minocycline, 2 due to tetracycline, and 1 due to doxycycline were identified. Eleven cases of SSLR due to minocycline, 3 due to tetracycline, and 2 due to doxycycline were identified. All 33 cases of drug-induced lupus were attributable to minocycline. Forty cases of SOD from minocycline, 37 cases from tetracycline, and 6 from doxycycline were detected. Hypersensitivity syndrome reaction, SSLR, and SOD occur on average within 4 weeks of therapy, whereas minocycline-induced lupus occurs on average 2 years after the initiation of therapy.

Conclusions: Early serious events occurring during the course of tetracycline antibiotic treatment include HSR, SSLR, and SOD. Drug-induced lupus, which occurs late in the course of therapy, is reported only with minocycline. We theorize that minocycline metabolism may account for the increased frequency of serious adverse events with this drug.

Arch Dermatol. 1997;133:1224-1230

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MINOCYCLINE HAS been reported to cause serious, rare adverse events including the hypersensitivity syndrome reaction (HSR), serum sicknesslike reaction (SSLR), and drug-induced lupus (DIL).[1,2] We conducted a review to determine if similar events are associated with other tetracycline antibiotics, namely, tetracycline and doxycycline. We also attempted to identify serious single organ dysfunction (SOD) attributable to these antibiotics.

RESULTS

Review of the Drug Safety Clinic database, Health Protection Branch data, and MEDLINE search produced 19 reports of HSR, 11 reports of SSLR, 40 reports of SOD, and 32 reports of DIL attributable to minocycline (**Table 1**).[2-34] **Table 2** shows data on the mean patient age, mean interval to onset of the reaction, and sex distribution of these reactions. We found no difference in the average daily doses of minocycline in causing the different reaction patterns. The most common patterns of internal organ involvement seen with minocycline HSR were hepatitis in 15 (79%), lymphadenopathy in 14 (74%), hematologic annormalities in 13 (68%), and renal and pulmonary abnormalities in 5 (26%) patients each. Three case fatalities have been described.[2,11] Three patients who were rechallenged redeveloped symptoms within 48 hours.

Reports of SOD attributable to minocycline include 17 of pneumonitis,[6,18-23] 4 of hepatitis,[3,24,25] 2 of antineutrophil cytoplasmic antibody–positive polyarthritis,[26,27] 1 of nephritis,[28] 1 of both fulminant hepatic failure and necrotizing pancreatitis,[29] and 1 of severe cutaneous adverse reaction.[30]

The patients with minocycline-induced lupus erythematosus presented with malaise that was accompanied by myalgia, arthralgia, or arthritis. Eighty-eight percent of cases occurred in women. Ten patients developed elevated serum hepatic transaminase levels. Two patients had livedo reticularis and antineutrophilic cytoplasmic antibodies, and in 2 other patients, precise descriptions of their erup-

MATERIALS AND METHODS

DEFINITIONS OF ADVERSE EVENTS

Specific reaction patterns were identified for inclusion. Hypersensitivity syndrome reaction was defined by fever, skin eruption, and internal organ involvement developing within 8 weeks of initiation of therapy; SSLR was defined by fever, skin eruption (most commonly urticarial or erythema multiforme), arthralgia with or without lymphadenopathy occurring within 6 weeks of treatment; and DIL was defined by the presence of antinuclear antibodies, the presence of at least 1 clinical feature of systemic lupus erythematosus (SLE) that resolves with drug discontinuation, and the absence of idiopathic SLE. Single organ dysfunction was defined as the presence of severe disease in a major organ, eg, pancreatitis, hepatitis.

SOURCES OF CASES

Drug Safety Clinic

We reviewed the records of all patients referred to the Glaxo Wellcome–Sunnybrook Drug Safety Clinic, Toronto, Ontario, from January 1985 through October 1996 who possibly had adverse events attributable to the use of minocycline, tetracycline, or doxycycline.

Health Canada

Reports from the Adverse Drug Reaction Monitoring Division of the Health Protection Branch, Ottawa, Ontario, were requested regarding adverse events possibly attributable to the use of minocycline, tetracycline, or doxycycline from 1966 through October 1996. Cases were classified as HSR, SSLR, DIL, or isolated SOD.

Literature Search

A thorough computer-based MEDLINE search of articles published from 1966 to October 1996 was conducted. Search terms included drug hypersensitivity, tetracycline antibiotics, and liver, kidney, skin, and joint diseases. The reference lists of all pertinent articles also were reviewed to identify any additional articles that might have been missed or that predated the computer search.

Utilization Data

The Institute of Medical Statistics, Toronto, provided us with the most recent statistics from 1994 to identify prescribing patterns for tetracycline antibiotics.

tion were lacking. No patient had renal, neurologic, or vasculitic involvement. All patients' symptoms had improved after discontinuation of the minocycline. Twenty-one patients who were rechallenged with minocycline developed a recrudescence of their DIL. One patient in whom symptoms developed with minocycline rechallenge remained asymptomatic after doxycycline exposure.[31]

Review of the Drug Safety Clinic database, Health Protection Branch data, and MEDLINE search produced 2 reports of HSR, 3 reports of SSLR, 37 reports of SOD, and no reports of DIL attributable to tetracycline.[35-41]

Review of the Drug Safety Clinic database, Health Protection Branch data, and MEDLINE search produced 1 report of HSR, 2 reports of SSLR, 6 reports of SOD, and no reports of DIL attributable to doxycycline.[42-45]

PRESCRIBING DATA

The Institute of Medical Statistics provided the most recent (ie, 1994) Canadian national statisitics regarding the use of tetracycline antibiotics. In 1994, 1 866 000 prescriptions for tetracycline antibiotics were filled (**Table 3**).

COMMENT

Minocycline has been used as successful, safe, long-term therapy for patients with acne vulgaris. However, there are concerns about the safety of minocycline based on recent reports of serious adverse events.[1,2] These reports of minocycline-induced side effects prompted a complete review of the literature to determine whether these reactions occur with other tetracycline antibiotics.

Twenty-two patients with HSRs attributable to the 3 tetracycline antibiotics were identified, of which minocycline was implicated in 86%. Reports of hepatotoxic effects from excessive serum levels of tetracycline are not included in this report as the mechanism of these reactions is associated with suprapharmacologic doses.[49-53]

Of note are additional references in the literature pertaining to tetracycline antibiotic–induced severe isolated SOD. These cases may represent a forme fruste of HSRs. For example, critical detailed information in case reports is often lacking so that the defining criteria of an HSR may not be fulfilled (eg, presence of fever). Another shortcoming with extracting data from case reports is that patients are often taking multiple medications and exact details of timing are missing. Therefore, an accurate assessment of drug causation is more difficult and less reliable.[54]

Isolated SOD attributable to tetracycline and doxycycline is manifest most commonly as severe cutaneous adverse reaction (30% and 71%, respectively), whereas SOD related to minocycline most commonly is manifest as pneumonitis (45%).

Based on the available information, there are more reports of serious adverse events from minocycline use than from the use of other tetracycline antibiotics. We acknowledge that the sources from which we collected our data rely on voluntary reporting, and therefore only a fraction of the true number of reactions are known. Although it is unclear why there are more serious adverse events reported with the use of minocycline, we theorize that this may relate to its unique metabolism.

Tetracycline antibiotics all possess the same basic

Table 1. Summary of Adverse Events to Tetracycline Antibiotics

	Tetracycline			Minocycline			Doxycycline		
	Drug Safety Clinic	Health Protection Branch	Literature	Drug Safety Clinic	Health Protection Branch	Literature	Drug Safety Clinic	Health Protection Branch	Literature
No. referred	166	976	...	17	160	...	39	145	...
Mild									
Rash	66	406	0	1	52	0	15	38	0
Urticaria	35	138	0	6	7	0	11	0	0
Angioedema	11	8	0	1	8	0	3	1	0
Photosensitivity	4	10	0	0	0	0	3	4	0
Vomiting/diarrhea	23	159	0	2	53	0	3	17	0
Severe									
Hypersensitivity syndrome reaction	0	1	1[46]	2	4	13[2,6-10,42,47]	0	0	1[42]
Serum sicknesslike syndrome	0	3	0	2	4	5[4,34]	1	1	0
Drug-induced lupus	0	0	0	1	0	32[2,3,5,12-17,27,31,32]	0	0	0
Single organ dysfunction	2	26	9	0	14	26	0	3	3
Severe cutaneous adverse reaction	1	9	1[35]	0	2	1[30]	0	1	3[43-45]
Hepatitis	1	7	0	0	7	4[3,24,25]	0	0	0
Pneumonitis	0	0	1[38]	0	0	17[6,18-23,33]	0	0	0
Pancreatitis	0	3	4[36,41,48]	0	1	1[29]	0	1	0
Nephritis	0	2	0	0	0	1[28]	0	1	0
Hematologic	0	4	2[39,40]	0	4	0	0	0	0
Parotitis	0	1	0	0	0	0	0	0	0
Myocarditis	0	0	1[37]	0	0	0	0	0	0
Arthritis	0	0	0	0	0	2[26,27]	0	0	0

4-ring carbocyclic structure but differ in the substituents on the ring[55] (**Figure**). Doxycycline has a hydroxyl side chain distinguishing this congener from tetracycline.[56] Minocycline shares the basic 4-ring structure of the other commonly used tetracyclines having a substitution of a dimethylamino group in the 7 position.[57] Whether minocycline metabolism produces a reactive metabolite is unknown, although an iminoquinone derivative may be generated that is a potential reactive electrophilic intermediate. Neither tetracycline nor doxycycline contains this amino acid side chain that has the potential to form this reactive metabolite.

Black pigmentation in the thyroid gland has been seen in patients receiving long-term minocycline treatment and is not seen with other tetracyclines. One explanation for this effect of minocycline is that its strongly electron-donating dimethylamino group possibly increases its reactivity to oxidation. In support of this theory, treatment of minocycline-induced black pigmentation with thyroid peroxidase resulted in the formation of a black product, whereas other members of the tetracycline family were not oxidized to dark products by the same system.[58]

In vitro studies have demonstrated the presence of a minocycline-glutathione conjugate when minocycline is incubated with hypochlorous acid, as is found in neutrophils. This in vitro system serves as a surrogate for oxidation reactions that take place in the liver. These reactions are most commonly mediated by the cytochrome P450 family of heme-containing enzymes. When a reactive metabolite is generated, there are several cellular mechanisms that detoxify this product. One such system is glutathione transferase; therefore, the presence of minocycline-glutathione conjugates implies the formation of potentially toxic metabolites. When tetracycline or doxycycline were incubated in the same system, no glutathione conjugates were detected (J. Uetrecht, personal communication, 1996).

The potential reactive metabolites generated by minocycline may bind to tissue macromolecules thereby causing cell damage directly, or they may act as haptens, eliciting an immune response secondarily.[59] This "hapten hypothesis" is thought to explain HSRs seen with aromatic anticonvulsants, sulfonamide antibiotics, allopurinol, and dapsone, as well as SSLRs due to cefaclor.[60]

Minocycline causes DIL and appears to be most common in young women. We found no reports of either tetracycline- or doxycycline-induced lupus. There has been a misperception that tetracycline causes DIL based on a misinterpretation of the 1959 article by Domz et al.[61] In that article, 1 of the 3 case reports describes aminoglutethimide-induced lupus erythematosus and another describes positive lupus erythematosus cells without clinical symptoms after tetracycline and penicillin were separately administered. The third case report describes a patient with active SLE whose underlying disease continued to progress after tetracycline was prescribed and in whom a severe cutaneous adverse reaction, possibly from tetracycline, developed. These cases do not support the concept of tetracycline causing DIL.

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