Question:

What is the incidence of Stevens-Johnson syndrome with roxithromycin?

Background

Question was asked by the Respiratory Consultant on my ward. A 66 year old woman was prescribed roxithromycin by her GP for a sore throat (suspected upper respiratory tract infection). Within 24 hours of taking roxithromycin, she developed fluid filled vesicles on her chest, shoulder and mouth. Her condition worsened the next day when the blisters spread and became haemorrhagic. She had developed lip desquamation and watery sore eyes, by the time she presented to the emergency department. A diagnosis of Stevens-Johnson syndrome possibly due to roxithromycin was made.

Other medical problems

Bronchopneumonia
Rheumatoid arthritis

Current medications are:

Celecoxib 200mg daily.

Summary.

No published reports of Stevens-Johnson syndrome associated with roxithromycin were found. However, other macrolide antibiotics such as erythromycin and azithromycin have been implicated as causes of Stevens-Johnson syndrome. The most compelling etiology of Stevens-Johnson syndrome in this patient is roxithromycin. The presence of mycoplasma or herpes simplex virus infection as causative agents can not be ruled out in this case.

Reply.

Stevens-Johnson syndrome is a severe form of erythema multiforme. The three most common causes of Stevens Johnson syndrome are infections due to herpes simplex virus (HSV), mycoplasma infection and drug reactions. In the clinical setting it is often difficult to establish a causal agent or precipitating cause.

I have not found any reports of Stevens Johnson syndrome associated with roxithromycin. However, other macrolide antibiotics such as erythromycin and azithromycin have been mentioned as possible causes of Steven Johnson syndrome. Skin patch tests done after patients experienced fixed drug eruptions with erythromycin, confirmed cross-reactivity with other macrolides. Therefore, if erythromycin or azithromycin cause Stevens Johnson syndrome, it may also occur with roxithromycin.

Case reports have documented the onset of Stevens Johnson Syndrome 16 to 48 hours after the patient started taking erythromycin. Target or iris lesions with mucosal vesicles and bullae are characteristic of the disorder. Prodromal symptoms of fever, headache, photophobia, malaise, cough and sore throat may be present for 1 – 14 days before lesions appear. The acute phase of Stevens Johnson syndrome typically reaches a nadir in 4 to 8 days. Cutaneous lesions heal after 1 to 3 weeks however, oral lesions can last for months. One case report has implicated azithromycin as the causative agent of Steven Johnson syndrome. The patient in this case developed Stevens Johnson syndrome after three
days of treatment with azithromycin. The patient tested negative for antibodies against HSV and mycoplasma pneumoniae. Skin tests using a scratch patch test with azithromycin induced a positive reaction.6

Another report described Stevens-Johnson syndrome in a set of 3 year old monozygotic twins who were treated for otitis media with erythromycin ethyl succinate and sulfisoxazole acetyl. The twin’s mother had an allergic reaction to erythromycin at the age of 17 and their maternal grandfather experienced a rash due to sulphonamides. HLA typing found the locus HLA-DR7 in all family members. This locus is implicated in immune complex mediated disorders such as Stevens-Johnson syndrome. A genetic predisposition for Stevens-Johnson syndrome was suggested.7

The most compelling etiology of Stevens-Johnson syndrome in our patient’s case is roxithromycin. There is a temporal association as the reaction began within 24 hours of our patient taking erythromycin. The only regular medication our patient was taking prior to her hospital admission was celecoxib and this has not been associated with Stevens-Johnson syndrome. However, the presence of mycoplasma or HSV infection as causative agents can not be ruled out in her case because no tests were conducted during her admission to eliminate these causes.

Treatment should focus on finding the causes and diagnostic tests should be conducted by cultures of lesions for herpes simplex virus and cold agglutinin titers for mycoplasma infection.1 Recent therapy recommendations have emphasized early corticosteroid administration in cases in which a drug reaction is suspected. The survival of some patients may depend on this therapy. The corticosteroids are usually given intravenously and suppress the inflammatory rejection of skin and mucous membranes until the inciting agent (the virus, drug or combination of the two) has been eliminated.7 Until the patient is cleared of suspected HSV infection intravenous acyclovir should be used. Supportive therapy with intravenous fluids is also indicated. Our patient was given amoxicillin and clavulanic acid (Augmentin) intravenously during her admission. Penicillins have been associated with the development of Stevens-Johnson syndrome. Therefore, the Augmentin had the potential to worsen the Stevens-Johnson syndrome and treatment with this drug should be discontinued.8

References

continued

References

SEARCH STRATEGY
1. BNF 47
2. Product Datasheet: (Romicin)
3. Martindale
4. Meylers
5. Micromedex
6. Reactions Database (ADIS)
7. Medline
8. Embase
9. CARM: contacted to find out if any other cases reported in NZ and reports in WHO database. (no response yet – they must be busy!)

Medline

Database: Ovid MEDLINE(R) <1966 to March Week 5 2004> Search Strategy:
--1 roxithromycin.mp. or exp Erythromycin/ or exp ROXITHROMYCIN/ (14052)
2 exp MACROLIDES/ (45303)
3 exp Drug Eruptions/ or exp Stevens-Johnson Syndrome/ or stevens johnson syndrome.mp. (11884)
4 (1 or 2) and 3 (109)
5 from 4 keep 8-9,13,16,18,21,25-26,31,35,41,46,48,72-73,76 (16)
6 from 5 keep 1-16 (16)

Embase

Database: EMBASE <1988 to 2004 Week 15> Search Strategy:
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1 roxithromycin.mp. or exp Erythromycin/ or exp ROXITHROMYCIN/ (25072)
2 exp MACROLIDES/ (45581)
3 stevens johnson syndrome.mp. or exp Stevens Johnson Syndrome/ (1597)
4 (1 or 2) and 3 (179)
5 from 4 keep 4,18,24,30,55,67-68,86,96,106,109,113 (12)

Outcome
Patient was given supportive therapy with intravenous fluids and intravenous hydrocortisone was commenced. Therapy with intravenous Augmentin was discontinued (after this answer was received). I reported this reaction to CARM in Dunedin and am awaiting follow-up from them. The consultant is writing this up as a case report. He commented that the background information provided by this answer was sufficient and he would add in more clinical details before submitting it as a case-report.