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Original Article

Information on Drugs Used in Management of Lepra Reactions in Commonly used Drug Information Sources in India

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Availability of adequate and proper drug information helps in rational prescription of essential drugs. This can be obtained from various sources such as National Formularies; other sources such as Current Index of Medical Specialties, Monthly index of medical specialties and the information available with the regulators and drug package inserts (PI). In this study, we assessed the drug information of the drugs used for treatment of both type of lepra reactions. Five drugs used for treating Lepra reactions were analyzed for any variation (Qualitative) in information on various parameters as mentioned in commonly used drug information sources such as CIMS India, MIMS India, Central Drugs and Standards Control Organization (CDSCO) website and National Formulary of India (NFI). We observed some gross qualitative variation regarding drug information given in different commonly used sources. Variation exists in the quality of information available on indications, contraindications, dosage and completeness of the dosing schedule about drugs available in various sources. As management of Lepra reactions is crucial in achievement desirable outcome of treatment of leprosy, it is important that information regarding drugs used for such indications should be 100% uniform in all commonly used and available sources.

Keywords : Drug Information, Irrational Drug Use, Lepra Reaction, Clofazimine, Thalidomide, Steroids

Introduction

The important part of treating a diagnosed disease is the proper prescription of drugs in its required dose, frequency and duration. This is the important part of rational prescription. If the drugs are used irrationally and inappropriately this may lead to suboptimal clinical benefit and possible adverse drug reactions (ADRs) (Singh et al 2016). So the knowledge on unbiased drug information helps in rational use of drugs. For obtaining knowledge on drug information various sources of information are used. The most

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important and commonly used are National Formularies (e.g. National Formulary of India (NFI), drug compendia such as Monthly Index of Medical Specialities (MIMS), Current Index of Medical Specialities (CIMS),and Package inserts (PIs) and medical/Pharmacological textbooks (Figueiras et al 2000, Lundborg et al 1998). There should be uniformity, reliability, and conforming to the regulatory label of the drug regarding drug information in various drug sources. Every country has approved indication(s) of the drug that was approved by the respective country regulators (Dresseret & Frader 2009, Radley et al 2006).

Approved indications of all the approved essential drugs are available with Government of India, Central Drugs and Standards Control Organization (CDSCO), which is India's national drug regulator (CDSCO 2018).

As management of Lepra reactions is crucial to outcome of treatment of leprosy, we planned the present study to assess this variation, if any, in a sample of anti-lepra reaction drugs with respect to various parameters given in various sources of drug information.

Materials and Methods

We analyzed the drug information of drugs used in managing lepra reactions (both type 1 reversal reaction/type 2 ENL reaction). The drugs commonly used in lepra reaction are Aspirin, Paracetamol, Prednisolone, Clofazimine and in special situation rarely Thalidomide (WHO 1998, Walker et al 2007). We assessed the information from various drug information sources CIMS India, MIMS India, National Formulary of India 2016 (NFI), and CDSCO website list. The parameters examined were - indication and dosage, contra indication, special precautions, adverse drug reaction, and pregnancy category were assessed. We also looked upon gross qualitative differences existing across various sources of drug information used in this study.

Table 1 : Scoring and interpretation

Score	Interpretation of information
0	Incorrect/Not available
1	Partially correct
2	Correct & insufficient
3	Correct/complete/sufficient

Statistical analysis : The information was extracted from various sources, tabulated and score were assigned for completeness of information's. The score were given for assessing the completeness of the information as 0, 1, 2 and 3 (Table 1). Results are presented as mean and percentages.

Results

Among the drugs Aspirin, Paracetamol and Prednisolone were used as anti-inflammatory and antipyretic for mild and moderate to severe cases. The information in CIMS India, MIMS India and NFI fulfilled all the important parameters as these drugs were the most commonly prescribed medicines for multiple indications and manufactured by multiple companies. The CDSCO website also fulfilled the indications regarding the above said three dugs.

The information regarding Clofazimine (Table 2) and Thalidomide (Table 3) in CIMS India, MIMS and NFI 2016 are tabulated below.

For Clofazimine, the indication in MIMS India is given generally as “lepra reaction” without any mention on “type of reaction”. Regarding dosage the information is partially only correct in CIMS India, NFI and insufficient in MIMS India. Regarding contraindication information is incorrect in MIMS India as Clofazimine is safest in pregnancy except for hyper pigmentation. Regarding pregnancy category information is not available with MIMS India.

Table 2 : Informations regarding Clofazimine

Parameters	CIMS INDIA	NFI	MIMS INDIA
Indication	Erythema nodosum leprosum (Type 2)	Type 2 lepra reactions.	Lepra reaction
Dosage	*Adult:* Treatment depends on severity. 100-200 mg daily for up to 3 mth. Doses >200 mg daily are not recommended. Gradually taper the dose to 100 mg daily as soon as the reactive episode is controlled. In general, continue with basic antileprosy treatment.	Lepra reaction: 200 mg daily for 3 weeks or as required.	300 mg daily for maximum of 3 months
Contraindications	Hypersensitivity. Lactation.	Lactation, renal and hepatic impairment.	Pregnancy, use effective contraception during and for atleast 4 months after stopping therapy
Special Precautions	Pregnancy. Patients with GI symptoms.	Pre-existing gastrointestinal symptoms (reduce dose, increase dose interval or discontinue if symptoms develop during treatment); liver and renal impairment; may discolour soft contact lenses; paediatrics, elderly, interactions	Hepatic or renal impairment H/o recurrent abdominal pain or diarrhoea. Lactation
Adverse Drug Reactions	Red-brownish black discolouration of skin Rash, pruritus, photosensitivity,	Reversible discolouration of skin, hair, cornea, conjunctiva, tears,	Nausea, giddiness, headache, diarrhoea with high doses, dryeyes, impaired

	diarrhea, nausea, abdominal pain, vomiting, weight loss, headache, drowsiness, dizziness, taste disorders, dryness of the skin, ichthyosis, and decreased tear and sweat production. Crystal deposited in the wall of small bowel mesenteric lymph nodes, liver and spleen. Severe abdominal symptoms including bowel obstruction, GI bleeding and splenic infarction.	sweat, sputum, faces and urine; dose-related gastrointestinal symptoms including pain, nausea, vomiting and diarrhea; severe mucosal and submucosal oedema, with prolonged treatment with high doses-may be severe enough to cause subacute small-bowel obstruction; pruritus, ichthyosis, elevated blood sugar, diminished vision, dizziness, eosinophillic enteropathy	vision, depression, GI, upset, tiredness, lymphadenopathy, dry skin, pruritus, red discolouration of conjunctivae, skin, hair & secretions, Eosinophic senteropathy, intestinal obstruction, splenic infarction, gastrointestinal bleeding and death, suicidal ideation, bulls eye maculopathy, QT prolongation
Pregnancy Category (US FDA)	**C**	**C**	-NA-

Table 3 : Information regarding Thalidomide

Parameters	CIMS INDIA	NFI	MIMS INDIA
Indication	Erythema nodosum leprosum (Type 2)	Erythema nodosum leprosum (ENL)	Skin manifestation associated with leprosy (erythema nodosum leprosum)
Dosage	***Adult:*** 100-300 mg once daily at bedtime, reduced gradually by 50 mg every 2-4 wk once a satisfactory response is achieved. Not for monotherapy if moderate or severe neuritis present. Max: 400 mg/day. Patients < 50 kg: Initially, 100 mg daily.	***Adult:*** For cutaneous ENL, thalidomide dosing should be initiated at 100 to 300 mg/day, Not for monotherapy if moderate or severe neuritis present. Max: 400 mg/day. Patients < 50 kg: Initially, 100 mg daily. Patients may then be tapered off medication	Initially 100-300 mg daily until signs & symptoms of active reaction have subsided, usually a period of atleast 2 weeks; then reduce dosage by 50 mg decrements every 2 to 4 weeks

		in 50 mg decrements every 2 to 4 weeks. Tapering off medication should be attempted every 3 to 6 months, in decrements of 50 mg every 2 to 4 weeks	
Contraindications	Pregnancy and lactation.	Hypersensitivity, pregnancy and lactation, interactions	Pregnancy and women of child bearing age, lactation
Special Precautions	All females of childbearing potential must use 2 reliable forms of contraception simultaneously 4 wk before starting therapy, during and 4 wk after therapy is discontinued. Therapy to be stopped immediately if pregnancy occurs. Male: Use of barrier methods of contraception if partner is of child-bearing potential. Patient should not drive or operate machinery. Discontinue therapy if any skin rash develops. Do not resume therapy if the rash is exfoliative, purpuric, or bullous, or if Stevens-Johnson syndrome or toxic epidermal necrolysis suspected.	During the period of treatment both males and females should take adequate means of contraception before, during and after (atleast 4 weeks) the therapy, therapy to be stopped immediately if pregnancy occurs; signs and symptoms of hypersensitivity include the occurrence of erythematous macular rash, possibly associated with fever, tachycardia, and hypotension, and if severe, may necessitate interruption of therapy, Serious dermatologic reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, seizures, impairment of mental and/or physical abilities required for the performance of hazardous tasks such as driving a car or operating complex machinery, potentiation	Children. bradycardia. contraceptive methods for atleast 4 weeks before treatment, during treatment, during dose interruptions and 4 weeks after treatment.

Adverse Drug Reactions	Severe and irreversible peripheral neuropathy, constipation, dizziness, orthostatic hypotension, drowsiness, somnolence, bradycardia, increase of viral load in HIV-infected patients, hypersensitivity reaction. Stevens-Johnson syndrome, toxic epidermal necrolysis and blood dyscrasias.	Teratogenicity, Drowsiness/somnolenc, peripheral neuropathy, constipation, dizziness, bradycardia, orthostatic hypotension, hypersensitivity, and neutropenia.	Teratogenicity, Drowsiness/somnolence, peripheral neuropathy, constipation, dizziness, bradycardia, orthostatic hypotension, hypersensitivity, and neutropenia, bleeding, DVT, pancytopenia, fever, asthenia, Interstial lung disease, pneumonia, bronchopeumopathy and risk of tumour lysis syndrome.
Pregnancy	X	X	-NA-

Table 4 : Scoring of the completeness of information regarding Clofazimine

Parameters	CIMS	NFI	MIMS
Indication	3 (100%)	3(100%)	2(66.67%)
Dosing	1(33.33%)	1(33.33%)	2(66.67%)
Contraindication	3(100%)	3(100%)	0(0%)
Special precautions	3(100%)	3(100%)	3(100%)
Adverse drug reaction	3(100%)	3(100%)	3(100%)
Pregnancy category	3(100%)	3(100%)	0(0%)
Total	16/18(88.87%)	16/18(88.87%)	10/18(55.55%)

Data represented in percentage.

Table 5 : Scoring of the completeness of information regarding Thalidomide

Parameters	CIMS	NFI	MIMS
Indication	2(66.67%)	3(100%)	2(66.67%)
Dosing	3(100%)	3(100%)	3(100%)
Contra-indication	3(100%)	3(100%)	3(100%)
Special precautions	3(100%)	3(100%)	3(100%)
Adverse drug reaction	3(100%)	3(100%)	3(100%)
Pregnancy category	3(100%)	3(100%)	0(0%)
Total	17/18(94.44%)	18/18(100%)	14/18(77.78%)

Data represented in percentage.

We did not identify any gross qualitative mismatch in the information across these three sources. Main discrepancies observed pertained to indication and dosing.

For Clofazimine, overall 88.87% of information was given in CIMS, NFI and 55.55% in MIMS. Among these, for indications 100% of information are given in CIMS, NFI and 66.67% given in MIMS. For dosing, only 33.33% information was given in CIMS, NFI and 66.67% for MIMS. Additionally the information for Clofazimine in contraindication is 100% incorrect regarding pregnancy.

For Thalidomide, 94.44% of information were given in CIMS, 100% in NFI and 77.78% in MIMS. Among these, for indications 100% of information is given in NFI followed by 66.67% given in CIMS and MIMS. For dosing information, 100% information were given in CIMS, NFI and MIMS.

Discussion

For successful management of Lepra reaction we should be aware about the drugs used in such condition and their management protocol. It is also important to know about the exact indication and the dosing of the drugs for rational prescription for clinical response with least or prevention of adverse effects. This drug information should be readily available to the managing physicians. In India the most common sources where such information is present includes package inserts, Formulary of India updated regularly and commercially published drug compendia such as Monthly Index of Medical Specialities and Current Index of Medical Specialities (Figueiras et al 2000, Lundborg et al 1998). For rational prescription anywhere in India the information provided should be uniform in respective to the regulators of drugs or the standard speciality textbook dealing the management of disease and the drugs dosage.

We undertook this study to assess quality of drug information available in various sources. The information about indications, dosing, contraindication, special precaution, adverse drug effects and pregnancy category was taken as the benchmark of overall drug information, and various sources were compared on the basis of this parameter. It was observed that no information on Clofazimine for lepra reaction management was available on the CDSCO website. Regarding Thalidomide indication information is insufficient and this drug was generally mentioned as part of leprosy management.

NFI, on the other hand, contained all requisite information on Thalidomide and 88.87% information for Clofazimine. NFI is mandated to include all the drugs in National List of Essential Medicines and some other commonly used drugs (NFI 2016). But with respect to Clofazimine dosing information was only partially correct.

MIMS is a commercially available drug information compendium and was found to be poor information provider among the other two compendiums. Overall it contains only around 55% information for Clofazimine and around 77% for Thalidomide. The information regarding contraindication in MIMS is totally incorrect.

This study highlights the discrepancies in drug information available in various sources by taking a representative sample of drugs used for Lepra reaction. To the best of our knowledge, this is the first study in India as well as rest of the south east countries, though parsimonious in design, an initiative taken to address the issue in variance of information. One limitation of this study is that, Package inserts which is also important drug information sources could not be collected and in pharmacy/medical shops there were non-available of package inserts.

Conclusion

Variation exists in the quality of information mainly on indications and dosing about lepra reaction drugs available in assessed sources. However, this information does not conform to regulatory benchmark all the time and specialty

management in special cases like lepra reactions. Exact/complete Information about drugs was not available in CDSCO website for lepra reaction. This should be seriously and urgently addressed as this is a part of national programme for a disease that is targeted for elimination by 2020. In such cases standard textbook(s) should be the bench mark for the indication with proper dosing and frequency.

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