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Prescription pattern & adverse drug reactions of prokinetics

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***Background & objectives*: Prokinetics are extensively prescribed leading to several adverse events (AEs). The aim of this study was to assess the prescription pattern in patients receiving prokinetics, and characteristics of adverse drug reactions (ADRs) in an outpatient department set up in a tertiary care hospital in western India.**

***Methods*: Patients attending outpatient departments of a tertiary care hospital and who had received prokinetic agent for at least seven days over the last one month were enrolled. Causality assessment of AEs was done and assessed for severity, preventability, seriousness and predictability.**

***Results*: A total of 304 patients [161 males (52.96%); 143 females (47.04%)] were enrolled. Most prescriptions (299/304, 98%) included domperidone, most commonly prescribed as fixed-dose combination (FDC) with pantoprazole (274/304, 90%). Prokinetic dose was not mentioned in 251/304 (83%) prescriptions, and 18/304 (6%) did not mention frequency. Of the 378 AEs reported from 179 patients (47.35%), 306 (81%) were mild, all non-serious; 272 (72%) not preventable and 291 (77%) predictable in nature. Decreased appetite (n=31, 8.2%) and fatigue (n=27,7.14%) were most commonly reported. Causality assessment by the World Health Organization-Uppsala Monitoring Centre scale showed that 180 AEs were related to suspected drug (17 probable and 163 possible ADRs). Significant correlation was observed for AEs with increasing number of drugs per prescription (Spearman's R=+0.8, *P*=0.05) and with increasing therapy duration (Spearman's R=+1.00, *P*<0.001).**

***Interpretation & conclusions*: Our findings showed that prokinetics were often prescribed as FDCs, with incomplete prescriptions. Domperidone was found to be associated with multiple AEs. It is suggested that regular prescription monitoring should be done in hospitals to encourage rational use of drugs.**

Key words Domperidone - gastric acid suppression - hypomotility - levosulpiride - prescription audit - proton pump inhibitor

Gastrointestinal (GI) motility may be impaired in many disorders such as functional dyspepsia, gastro-oesophageal reflux disease, gastroparesis (idiopathic or diabetic) and chronic idiopathic constipation[1]. There is considerable evidence to suggest an association between motility disorder and symptom production in functional dyspepsia[2,3]. The management of patients with GI hypomotility usually includes administration of prokinetic agents[1]. The various prokinetic agents used clinically are mainly the

dopamine antagonists (metoclopramide, domperidone, levosulpiride and itopride) and the serotonin (5-HT) receptor agonists (5HT4 agonists such as cisapride and mosapride)[4].

Though the efficacy of all the prokinetic agents for the treatment of GI hypomotility disorders is a known fact, these agents are associated with many adverse effects. The main side effects of metoclopramide include extrapyramidal symptoms such as dystonia, akathisia, parkinsonism-like symptoms and tardive dyskinesia. These appear to occur more commonly in children and young adults and at higher doses. Metoclopramide also can cause galactorrhoea by blocking the inhibitory effect of dopamine on prolactin release, but this adverse effect is relatively infrequent, albeit of major concern to females[4]. Levosulpiride is a therapeutic option in the management of functional dyspepsia on the basis of dopaminergic pathways controlling GI motility[5]. On the other hand, the serotonergic component of levosulpiride may enhance its therapeutic efficacy in functional dyspepsia[6]. However, it is associated with various side effects such as extrapyramidal symptoms, sedation, drowsiness, postural hypotension and increased level of prolactin associated with galactorrhoea and breast engorgement[7]. As domperidone does not cross blood-brain barrier, it does not cause any extrapyramidal adverse effects. However, since the pituitary gland lies outside the blood-brain barrier, it causes increase in prolactin levels leading to galactorrhoea and breast engorgement[4]. Itopride is well tolerated with a few minor adverse drug reactions (ADRs) such as diarrhoea, headache and abdominal pain[8]. Cisapride, due to QT segment prolongation, increases the risk of arrhythmia and risk of sudden death[9].

Thus, prokinetic agents, though effective in hypomotility conditions, are associated with multiple adverse effects. Many times, their use has been rampant without a valid indication as many are available easily without prescription. Thus, the present study was carried out to assess the prescription pattern, find the rate of occurrence of associated adverse events (AEs), determine their causality and analyze their severity, seriousness, preventability and predictability in patients receiving any prokinetic agent from the outpatient departments (OPDs) of a tertiary care teaching hospital in western India.

Material & Methods

This present observational study was initiated in the department of Pharmacology & Therapeutics, Seth GS Medical College and KEM Hospital Mumbai, India, after approval from the Institutional Ethics Committee (EC/OA-53/2015). Written informed consents from patients or legally acceptable representatives were obtained. Adult patients (18-65 yr of age), of either gender, attending medical gastroenterology and ear-nose-throat (ENT) OPDs of the hospital and received any prokinetic agent for at least a period of seven consecutive days in the past one month, were enrolled. The study duration was pre-specified to be six months (January-June 2016). Data were analyzed in the following two months (July-August 2016). A duration specific convenience sampling method was adopted. A pre-designed case record form was used to collect relevant data, which included demographic details, prescription details pertaining to drug name, dose, route, frequency, duration and indication of use (all for both the prokinetic agents and concomitant medicines), working diagnosis and information regarding any AE. Patients' detailed history about both disease and drug therapy was noted carefully from previous medical records, and information regarding possible adverse effects was collected from the patients. If the previous medical records were not available with the patients, they were excluded from the study. From these data, causality assessment was done using both World Health Organization-Uppsala Monitoring Centre (WHO-UMC) Scale[10] and Naranjo algorithm[11]. All the AEs were further assessed and classified according to severity (modified Hartwig-Siegel scale[12]), preventability (Schumock-Thornton criteria[13]), seriousness[14], predictability, pattern and involvement of organ system [WHO-Adverse Reactions Terminology (ART) organ system classification code[15]].

Statistical analysis: Data were analyzed using descriptive statistics by SPSS v 21.0 (IBM Corporation, Armonk, NY, USA). Chi-square test and Fisher's exact test were applied to categorical data and Spearman's correlation was applied to continuous data.

Results

A total of 304 patients [161 males (52.96%) and 143 females (47.04%)] were included in the study. The mean age of the enrolled patients was 39 ± 12.2 yr. Of the 304 prescriptions analyzed, 298 (98%) included domperidone, and most commonly, it was prescribed as a fixed-dose combination (FDC) with pantoprazole (274/304, 90%). Levosulpiride was also prescribed as another prokinetic agent in combination with pantoprazole (Fig. 1). Dose of the prokinetic agent

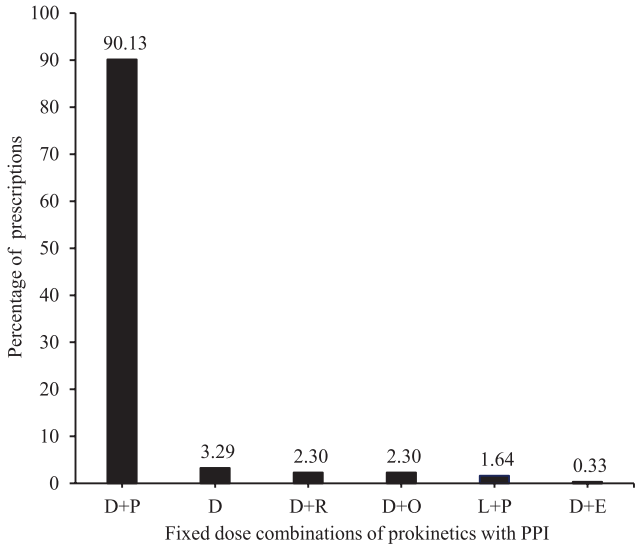

Fig. 1. Number of prescriptions with different prokinetic agents, single or in combination (n=304). D, domperidone; P, pantoprazole; R, rabeprazole; O, omeprazole; L, levosulpiride; E, esomeprazole; PPI, proton pump inhibitor.

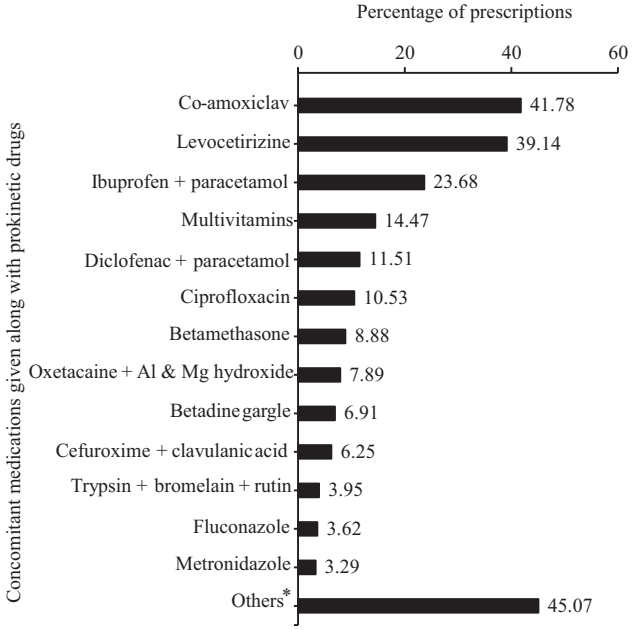

Fig. 2. Percentage of prescriptions with concomitant medications. *Others include cefixime, betadine gargle, ondansetron, probiotics, doxofylline, iron+folic acid, clotrimazole ointment, clonazepam, proton pump inhibitors, ranitidine, betahistine, mebendazole, metoprolol, cetirizine, chlorpheniramine maleate, chlorhexidine mouthwash, mucaine gel, salbutamol metered dose inhaler, oxymetazoline nasal drops, hyoscine, furosemide, levofloxacin, anti-tuberculosis drugs, doxycycline, mupirocin ointment, aspirin, calcium, pyridoxine, phenytoin, rifaximin.

was not mentioned in 251 (83%) prescriptions. Where mentioned, the strength of domperidone was 30 mg along with 40 mg of pantoprazole as FDC. Most of these (239 of 304, 79%) were prescribed as once daily dosing, a few were prescribed as twice (44 of 304, 14%) or thrice daily (3 of 304, 1%) as well; whereas six per cent (18 of 304) prescriptions did not mention the frequency. In most of the cases, prokinetics were prescribed for up to seven days (69%, 211 of 304) with a maximum of 45 days in one patient (a case of liver cirrhosis with regurgitation). Four prescriptions lacked any mention of duration.

The prescriptions were further analyzed to find the common drugs being prescribed along with prokinetics (Fig. 2). Most common was amoxicillin+clavulanic acid (127 of 304, *i.e*. 42% of total prescriptions) followed by levocetirizine (119 of 304, *i.e*. 39%) and non-steroidal anti-inflammatory drugs combinations (ibuprofen or diclofenac combined with paracetamol; total 107 of 304, *i.e*. 35%). The total number of drugs prescribed in 304 patients was 690. When prescribing pattern of these concomitant medications was analyzed, incompleteness was found in terms of dose not mentioned in 68 per cent (472 of 690), frequency not mentioned in 5.5 per cent (38 of 690) and duration not mentioned in 9.5 per cent (66 of 690) of total drug prescriptions. Half of the prescriptions contained three drugs (152 of 304, 50%), followed by four drugs (70 of 304, 23%), two drugs (50 of 304, 16%) and five drugs (29 of 304, 9%). One prescription contained only one drug (domperidone+pantoprazole FDC) and two prescriptions contained six drugs (both were cases of chronic suppurative otitis media; antibiotic/analgesic/anti-inflammatory/antihistaminic and multivitamin were co-prescribed).

Of the total 304 patients, at least one AE was noted in179 patients (58.8%). A total of 378 AEs were reported from these 179 patients (90 males), which were considered for causality assessment and further analysis. When occurrence of AE was compared amongst different age groups and genders, no significant difference was observed. However, a significant positive correlation was observed for occurrence of AEs in terms of increasing number of drugs per prescription (Spearman's Rho correlation coefficient, R=+0.8 and two-tailed P=0.05) and with increasing duration of therapy (Spearman's Rho correlation coefficient, R=+1.00, P<0.001). It was found that the occurrence of AEs was significantly higher in those patients receiving three or more drugs concomitantly than those receiving one or two (P<0.001). Sixty six prescriptions were found to have multiple ADRs.

Table I. Causality assessment of reported adverse events (n=378)

Description	WHO-UMC scale[10] (n=378)	Naranjo algorithm[11] (n=378)
Certain/definite	0	0
Probable (%)	17 (4.49)	17 (4.49)
Possible (%)	163 (43.12)	160 (42.32)
Unlikely/doubtful (%)	198 (52.38)	201 (53.17)
Conditional/unclassified	0	NA
Un-assessable/unclassifiable	0	NA

WHO-UMC, World Health Organization-Uppsala Monitoring Centre; NA, not applicable

Causality assessment by WHO-UMC scale revealed 180 AEs to be causally related to the suspected drug (17 probable and 163 possible ADRs). Assessment by Naranjo scale revealed similar results with 177 AEs being causally related to the suspected drug (17 probable and 160 possible ADRs). Rest of the AEs (198 by WHO-UMC and 201 by Naranjo scale) were designated as unlikely/doubtful after causality assessment (Table I). Both the scales were compared to find out the strength of agreement between them using Cohen's kappa statistical measurement and were found to be with strong agreement (98.4%) and a kappa value of 0.971 (standard error=0.012, 95% confidence interval=0.947-0.994). Severity assessment by modified Hartwig-Siegel scale revealed that 81 per cent (306 of 378) of the recorded AEs were mild and rest (72 of 378, 19%) were moderate in nature. None of the documented AEs was found to be severe or serious in nature. Preventability assessment by Schumock-Thornton criteria revealed that 72 per cent AEs (272 of 378) were not preventable, while the remaining 28 per cent (106 of 378) were preventable in nature, of which four AEs were definitely preventable and 102 AEs were probably preventable. Most of the AEs (291 of 378, 77%) were found to be predictable (type A or augmented) in nature; rest were non-predictable (type B or bizarre). Analysis of these AEs revealed that decreased appetite was most commonly associated with prokinetic use (31 of 378, 8%) followed by fatigue, throat pain/irritation, sedation/drowsiness, headache, diarrhoea, oral ulcers and ear discharge (Table II). Menstrual irregularity (usually long cycles) was reported in nine women, and five women reported breast tenderness; all were in patients receiving domperidone. All the five patients who received levosulpiride experienced AEs in the form of fatigue, headache and abdominal fullness. When AEs were analyzed according to the WHO-ART organ system classification code, GI system (WHO-ART code: 0600) was the most commonly affected organ system (129 of 378, 34%), followed by general body as a whole (code: 1810, 84 of 378, 22%) and neurological system (code: 0400, 56 of 378, 15%) (Fig. 3).

Table II. Common types/pattern of reported adverse events (n=378)

Adverse event	n (%)
Decreased appetite	31 (8.2)
Fatigue	27 (7.14)
Throat pain	27 (7.14)
Sedation/drowsiness	25 (6.61)
Headache	22 (5.82)
Diarrhoea	20 (5.29)
Ulcers (oral/palatal/lower lip)	18 (4.76)
Ear discharge	18 (4.76)
Throat irritation	18 (4.76)
Nausea	15 (3.96)
Abdominal pain	14 (3.70)
Constipation	12 (3.17)
Dizziness	11 (2.91)
Dysphagia	11 (2.91)
Running nose	11 (2.91)
Menstrual irregularity	9 (2.38)
Regurgitation	8 (2.11)
Body ache	7 (1.85)
Hoarseness of voice	7 (1.85)
Ear ache	6 (1.58)
Breast tenderness	5 (1.32)
Others	56 (14.82)

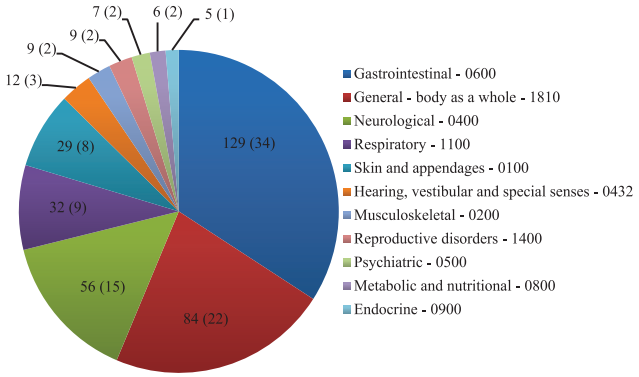

Fig. 3. Distribution of adverse events according to the World Health Organization-Adverse Reactions Terminology Organ System Classification Code[15] (n=378). Absolute number of adverse events is provided in the pie chart followed by percentage in parenthesis.

Discussion

The WHO defined rational use of drugs as patients receiving medications appropriate to their clinical needs, in doses that meet their individual requirements, for an adequate period of time and at the lowest cost to them and their community[16]. The WHO and the International Network of Rational Use of Drugs have developed a set of drug prescribing indicators to be used as measures of prescribing performance in healthcare settings[17]. The evaluation of quality of medical care provided in a particular set-up is called medical audit and prescription audit is a part of it, which seeks to monitor, evaluate and if necessary suggest modifications in the prescribing practices of medical practitioners, and thus considered as a useful approach to achieve the objective of improving the quality of patient care[18,19].

Prescription audits in different setups have many times showed the lack of completeness, legibility and rationality. Studies[19-21] have found flaws in prescribing while analyzing the pattern of the same in their institutions. Incompleteness in prescribing prokinetic agents and concomitant medications were observed in our study. Dose of the prokinetic agent was not mentioned in 83 per cent of the prescriptions, six per cent prescriptions did not mention the frequency and three per cent prescriptions lacked any mention of proposed duration of therapy. As a result, the prescribed daily dose versus the defined daily dose could not be calculated and compared. Similarly, when prescription pattern of concomitantly administered medications were analyzed, incompleteness was found in terms of dose not mentioned in 68 per cent, frequency not mentioned in 5.5 per cent and duration not mentioned in 9.5 per cent prescriptions.

Although symptom relief rates were found to be significantly higher with levosulpiride group as compared to domperidone and metoclopramide[22], yet in our study, domperidone was the most commonly prescribed prokinetic and was usually prescribed as a FDC with pantoprazole. This was probably because domperidone is less expensive as compared to other prokinetic drugs and is freely available from hospital formulary. John *et al*[23] found metoclopramide as the most frequently utilized prokinetic agent in critically ill patients from a tertiary care hospital in south India, though in our study none of the patients received metoclopramide. Increased use of domperidone over other prokinetics in paediatric age group was observed by Mt-Isa *et al*[24].

Approximately 59 per cent of the patients who received prokinetic agents showed one or more AEs, which were subjected to causality assessment and further analysis. It was decided to use both WHO-UMC scale and Naranjo algorithm as there is no gold standard for causality assessment, and therefore, one scale cannot be preferred over the other. Both of these are widely used causality assessment tools, but none has been validated so far to give acceptable reproducible results[25]. The scales showed 'very good' strength of agreement (98.4%) in assessing causality by Cohen's kappa statistical measurement (kappa value of 0.971). Belhekar *et al*[25] reported poor agreement between the two scales while Mittal and Gupta[26] reported a moderate to good agreement. Such variations in different settings are expected as skill of assessing the causality may vary based on knowledge, experience and interpretation of the personnel assessing the causality.

Most of the AEs were mild (81%) and non-serious (100%) in nature. Of the 89 women in whom AEs were detected, nine reported menstrual irregularity (usually delayed menstruation) and five reported breast tenderness. Galactorrhoea has also been reported as AE of domperidone[27,28].

Nearly one-third (28%) of the AEs were preventable in nature. For example, in a few cases, appropriate history-taking and the absence of a definite indication would have prevented the irrational administration of the prokinetic agent and the subsequent ADRs. Preventable ADRs are a major burden on the healthcare system, so more careful and vigilant choice and administration of prokinetic agent are needed on the part of the physicians. Majority of the AEs (77%) were found to be predictable or Type A (augmented) reactions in nature, thought to be an extension of the pharmacological profile of the drugs. It has been stated that in general, for type B reactions, the drug needs to be discontinued[29], but in the present study, the offending drugs were not withdrawn even in the cases of type B reactions as those AEs were mild and non-serious in nature.

The present study had some limitations. It was based on data from only two OPDs; hence, the findings cannot be generalized to other setups and there is a need to extend it to the remaining clinical departments. It was a cross-sectional study, and hence, a follow up study needs to be undertaken to capture delayed AEs. Prescriptions were mostly restricted as

per the availability of the drug in the hospital; further analysis needs to be extended to other prokinetics. A chance of recall bias was there which should be kept in mind.

In conclusion, our findings showed that the prokinetic drugs were rampantly prescribed drugs in FDCs and with incomplete prescriptions, and many of the receivers experienced multiple AEs. There should be regular prescription audits and physicians should be encouraged about rational use of drugs. Further, there should be a highly efficient pharmacovigilance programme in place along with patient awareness activities to prevent and report the AEs.

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***Conflicts of Interest*:** None.

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