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Use and Abuse of Anti-Ulcerants: A Perspective from Bangladesh

S.M. Yasir Arafat[1], Md. Jahid Hasan[2], Russell Kabir[3]
[1]Department of Psychiatry, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
[2]Dhaka Medical College, Dhaka, Bangladesh
[3]Senior lecturer, Department for Allied and Public Health, Anglia Ruskin University, Chelmsford, Essex, UK

Commentary Report

Proton pump inhibitors (PPIs) is a time-tested drug for effective suppression of gastric acid and is indicated in several upper gastrointestinal disorders [1]. These drugs irreversibly inhibit the gastric H+, K+ ATPase pump and reduce both basal and stimulated gastric acid output [2]. They are shown to be effective in the treatment of gastro-esophageal reflux disease (GERD), peptic ulcers, and dyspepsia [3-6]. Along with antibacterial, they are used for the eradication of *Helicobacter pylori* [7]. PPIs are also prescribed as a concomitant medication to prevent non-steroidal anti-inflammatory drug (NSAID) associated ulcers in high-risk patients and also patients who receive Glucocorticoid for prolonged duration [8]. There are two main indications for long-term use of PPIs are reflux disease and use of maintenance non-steroidal anti-inflammatory drugs (NSAIDs), which puts patients at risk for non-steroidal gastropathy. Except for hyper secretory states, which are very rare disorders, most other indications for acid suppression do not require years and years of PPI exposure [9].

The National Institute for Health and Clinical Excellence (NICE) published its guidelines on proton pump inhibitors in 2000 [10]. Its recommendations for using these drugs—particularly in the long term—are relatively selective. In spite of limited prescribing recommendation, rise of PPI usage is far beyond a change in morbidity [11]. These are frequently prescribed without a clear indication and for a longer period than recommended [12]. Although it might be assumed that overprescribing occurs mainly in primary care but inappropriate use of PPI in secondary care is also abundant [10]. In hospital inpatients taking proton pump inhibitors in Australia [13], Ireland [14], and the UK [12], 63%, 33%, and 67% of patients did not meet their country's criteria for taking the drug. In a series of hospital inpatients in Michigan, USA, 20% of patients were taking a proton pump inhibitor on admission and another 40% were prescribed the drug during their hospital stay (mostly for prophylaxis). At discharge, half the patients were taking a proton pump inhibitor—more than double the number who were taking the drug when admitted [15]. Another study from New Zealand found that 40% of hospital inpatients were taking proton pump inhibitors inappropriately [16]. Two thirds of these patients were still taking the drugs on discharge and most were still taking them six months later. In a Swedish cohort of patients who had been taking proton pump inhibitors for four years, 27% were able to discontinue the drug altogether [17]. A prospective audit of a series of patients admitted as a medical emergency to a hospital in Wales found that a quarter of patients were taking a proton pump inhibitor. In only half of the patients was the indication for the drug deemed appropriate [18]. Though fewer data is available to our country it can be assumed that situated is almost same in Bangladesh.

PPI are relatively safe and less toxic in comparison to other drugs but it is not free from side effects and cannot be overlooked. The long-term use of PPIs is associated with a higher risk of community acquired pneumonia, osteoporosis and hip fractures [19-20]. Another important recognized consequence of prolonged use is acute interstitial nephritis and pseudomembranous colitis [19]. An increase in the prevalence of pneumonia and *Campylobacter* enteritis is reported, as well as a doubling of the risk of infection with *Clostridium difficile* [21]. Investigators around the world have published many studies looking at longer-term exposure among patients may increase the risk of hepatotoxicity, nephrotoxicity, or other unusual side effects but fortunately incidence is not so common. More common potential adverse effects relating to the two known class effects of PPIs: Hypochlorhydria and

Hypergastrinemia [22]. Rebound secretion of Hydrochloric acid after discontinuation of drug may potentiate increase sensation of burning and lead to further consumption of PPI22. Moreover, several investigations had shown the strong association of iron deficiency anemia with prolonged use of PPI which may be fatal if untreated [23].

Besides side effect profile it causes enormous burden of health expenditure throughout the world. In United Kingdom, they constitute the largest expenses for any single drug group [24]. In 2006, expenditure on these drugs was £425m (€595m; $872m) in England [25]. Germany has resulted in an annual spend of € 927 million (i.e. $ 1.2 billion) in 2010 and £7bn globally [26]. Bangladesh is a densely-populated country with significant health related Millennium Development Goals (MDGs) with progressive pharmaceuticals sector mostly driven by anti-ulcerants [27-33]. The current market size is about 14 billion with having almost persistently double-digit growth. There are 267 licensed pharmaceutical companies and the market is almost self-sufficient in meeting local demand as 97% of the drugs are manufactured locally [27-33]. Anti-Ulcerants are significantly dominating the huge volume sells with marked impact on company revenue. Recent tradition shows, anti-ulcerants as a therapeutic class tops the whole market with having about 15% of the total market share. Moreover, brand wise ranking based on sales volume shows among the top 25 brands, there are 11 anti-ulcerant brands with the top 4 anti-ulcerant brands [33]. Yet studies consistently show that proton pump inhibitors are being overprescribed worldwide in both primary and secondary care. Between 25% and 70% of patients taking these drugs have no appropriate indication. This means that, at the very least, £100m from the National Health Service (NHS) budget and almost £2 bn worldwide is being spent unnecessarily on proton pump inhibitors each year and it could be saved if proper utilization can be maintained [10].

Table 1: Top Anti-Ulcerant brands with their rank in pharmaceutical sells in Bangladesh [32].

S.N.	Brand	Generic	Rank
1	SECLO	Omeprazole	1
2	MAXPRO	Esomeprazole	2
3	SERGEL	Esomeprazole	3
4	PANTONIX	Pantoprazole	4
5	LOSECTIL	Omeprazole	6
6	NEOTACK	Ranitidine	9
7	FINIX	Rabeprazole	11
8	EXIUM	Esomeprazole	13
9	NEOCEPTIN R	Ranitidine	20
10	XELDRIN	Omeprazole	23
11	ENTACYD PLUS	Antacid	25

Source: DOE report, 2012.

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