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comparing fondaparinux to enoxaparin in the orthopedic setting. Second, the Food and Drug Administration (FDA) reviews of data and trials submitted by GlaxoSmithKline in support of fondaparinux's approval in which enoxaparin was used as the active control in orthopedic procedures.

COMPARATIVE REVIEW OF FONDAPARINUX (ARIXTRA) AND ENOXAPARIN (LOVENOX) FOR USE IN ORTHOPEDIC PROCEDURES

by

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This evaluation examines the safety and efficacy of fondaparinux (Arixtra) compared to enoxaparin (Lovenox) in the orthopedic procedures of knee and hip replacement and hip fracture surgery. The evidence included in this evaluation is limited to two sources. First, published randomized controlled trials (RCTs) directly

INTRODUCTION

The synthetic pentasaccharide fondaparinux was approved by the FDA on December 7, 2001 for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism. Enoxaparin has similar FDA approved orthopedic indications; however, it is not approved for prophylaxis of DVT in patients undergoing hip fracture surgery.

In terms of pharmacologic activity, fondaparinux exerts its antithrombotic effects via antithrombin III-mediated selective inhibition of Factor Xa. This neutralization of Factor Xa disrupts the blood coagulation cascade inhibiting thrombin formation and thrombus development.¹ In comparison, enoxaparin is a low molecular weight heparin with a higher ratio of anti-Factor Xa to anti-Factor IIa activity compared with unfractionated heparin.²

With regard to FDA approved dosing for prophylaxis of deep vein thrombosis, 2.5 mg of fondaparinux is given subcutaneously once daily beginning six to eight hours after surgery for a typical course of five to nine days.¹ In comparison, the recommended dose of enoxaparin for prophylaxis of DVT after hip or knee replacement surgery is 30 mg subcutaneously every 12 hours beginning 12 to 24 hours after surgery. An alternative dosing regimen in hip replacement surgery is 40 mg enoxaparin given subcutaneously once daily beginning 9 to 15 hours prior to surgery. Continued thromboprophylaxis with daily 40 mg subcutaneous enoxaparin is recommended for three weeks in hip replacement patients, although the usual duration of use is seven to ten days. Dose adjustment to 30 mg subcutaneous once daily enoxaparin sodium is required in patients with severe renal impairment (creatinine clearance < 30mL/min) undergoing hip or knee replacement surgery.² Fondaparinux is contraindicated in patients with severe renal impairment (creatinine clearance < 30mL/min) and in patients weighing less than 50 kg for prophylactic use.¹

METHODS

The National Library of Medicine's PubMed database was searched using "enoxaparin"[MeSH] AND "fondaparinux"[Substance Name] as search terms. The search was limited to English, Human, and Randomized Controlled Trial articles. A total of 6 studies were identified

using the above criteria and further limited to orthopedic indications.

Also included in this evaluation are the FDA reviews of data and clinical trials submitted to the FDA in support of fondaparinux's approval. These reviews can be found on the FDA's Web site at http://www.fda.gov/cder/foi/nda/2001/21-345_Arixtra.htm.

Studies and articles published in medical journal supplements, throwaway journals, and published abstracts were excluded. Evidence suggests that RCTs published in journal supplements are generally of inferior quality compared with articles published in the parent journals.³ Throwaway journals are characterized as those that contain no original investigations, are provided free of charge, have a high advertisement-to-text ratio, and are non-society publications. They have been found to be lower in methodologic and reporting quality than journals containing original investigations.⁴ Published abstracts are also excluded from review as only approximately one half of all studies initially presented in abstract form may subsequently be published as full-length reports.^{5,6}

RESULTS

Table 1 below summarizes the published RCTs included in this evaluation of fondaparinux and enoxaparin in the prophylaxis of DVT within the context of hip replacement surgery, hip fracture surgery, and knee replacement surgery.

Primary efficacy measures in these trials included incidence of venous thromboembolic events (VTE), incidence of DVT, and incidence of fatal and non-fatal

pulmonary embolus (PE). NV Organon and Sanofi-Synthelabo, the developers of fondaparinux, sponsored all published trials.

Table 1 – Randomized Controlled Trials Comparing Fondaparinux to Enoxaparin in the Prophylaxis of Deep Vein Thrombosis for Orthopedic Indications: Efficacy Results				
Study, Surgery	N, Treatment Groups	Duration / Follow-up	Efficacy Endpoints (Incidence)	P value(s)
Eriksson BI, et al. ⁷ Hip fracture	1711 (a) 2.5 mg SC daily fondaparinux 6 hrs post-op (b) 40 mg SC daily enoxaparin 12 hrs pre-op	(a) 11 days (b) 11-49 days follow-up	VTE: (F) 52/626 (8.3%) (E) 119/624 (19.1%) DVT: (F) 49/626 (7.8%) (E) 117/624 (18.8%) PE: (F) 3/626 (0.5%) (E) 3/624 (0.5%) VTE: (F) 13/831 (1.6%) (E) 9/840 (1.1%) DVT: (F) 7/831 (0.8%) (E) 2/840 (0.2%) Non-fatal PE: (F) 3/831 (0.4%) (E) 3/840 (0.4%) Fatal PE: (F) 5/831 (0.6%) (E) 5/840 (0.6%)	<0.001 <0.001
Lassen MR, et al. ⁸ Hip replacement	2309 (a) 2.5 mg SC daily fondaparinux 6 hrs post-op (b) 40 mg SC daily enoxaparin 12 hrs. pre-op	11 days	VTE: (F) 37/908 (4.1%) (E) 85/919 (9.2%) DVT: (F) 36/908 (4.0%) (E) 83/919 (9.0%) PE: (F) 2/908 (0.2%) (E) 2/919 (0.2%)	<0.001 <0.001
Turpie AG, et al. ⁹ Hip replacement	2275 (a) 2.5 mg SC daily fondaparinux 6 hrs post-op (b) 30 mg SC twice daily enoxaparin 18 hrs post-op	(a) 11 days (b) 11-49 days follow-up	VTE: (F) 48/787 (6.1%) (E) 66/797 (8.3%) DVT: (F) 44/787 (5.6%) (E) 65/797 (8.2%) PE: (F) 5/787 (0.6%) (E) 1/797 (0.1%) VTE: (F) 19/1126 (1.7%) (E) 12/1128 (1.1%) DVT: (F) 13/1126 (1.2%) (E) 10/1128 (0.9%)	0.099 0.047 0.122

Of the trials appearing in Table 1, study DRI 2643 appears to have never been published. The FDA medical officer noted in comments concerning this study the suggestion that increasing fondaparinux dose was associated with increasing major and minor hemorrhage rates. As a result of bleeding events, the 6.0 mg and 8.0 mg doses were terminated during the conduct of this trial.¹¹

EFFICACY CONCLUSION

Overall efficacy results from the clinical trials submitted to the FDA in the approval of fondaparinux suggest that the drug is, at a minimum, as effective as enoxaparin in the prophylaxis of DVT for orthopedic indications. The FDA medical officer recommended, however, that no claims of superiority could be made over enoxaparin for the following reasons: (1) hip replacement study EFC2442 demonstrated no significant difference in the incidence of VTE between the two treatment groups, (2) in study 63118 (hip replacement) enoxaparin was administered in a suboptimal regimen as only 88 percent of patients received the drug pre-operatively and at 40mg SC once daily. The FDA approved and recommended dosage of enoxaparin for prophylaxis of DVT within this setting is 30 mg SC every twelve hours post-operatively, (3) most patients in the knee replacement study (095-002) received the first dose of enoxaparin at the later part of the recommended time range

(21+/-3hrs) after surgery than what may be ideal for prophylaxis (12-24 hours), which may have influenced findings in favor of fondaparinux.¹² No significant differences were seen across all studies in the incidence of PE between the two drugs, which again suggests similar efficacy for this endpoint.

Fondaparinux is FDA approved for use in hip fracture surgery while enoxaparin does not. This may be an important factor to consider within individual practice settings where an increased number of hip fracture surgeries are being performed. However, fondaparinux also presents drawbacks to use including contraindication in severe renal impairment (creatinine clearance <30mL/min) and in patients weighing less than 50kg in prophylactic use, while dose adjustment can be performed with enoxaparin. This may limit the usefulness of fondaparinux in clinical settings even if it has similar efficacy as enoxaparin and less frequent dosing. In light of all major orthopedic surgeries as a whole, fondaparinux may not offer a significant advantage in terms of efficacy and flexibility of use in in-patient settings as compared with enoxaparin for prophylaxis of DVT.

COMPARATIVE SAFETY – BLEEDING

The FDA medical officer review of fondaparinux's safety noted that the major safety concerns identified in pre-clinical and phase I,

II, and III testing were a long half life, renal excretion, bleeding risk, thrombocytopenia, heparin antibodies, and skin reactions.

The medical officer noted that more than 3,600 patients were treated with fondaparinux in phase II and III clinical trials in the orthopedic setting. All of these patients had nearly normal renal function (serum creatinine < 2.0 mg/dl) and the majority was treated for 5 to 9 days, maximum 11 days, with fondaparinux 2.5 mg daily. The major safety adverse event observed was bleeding.¹³

The overall bleeding rate associated with fondaparinux was higher compared to enoxaparin, 5.7 percent and 4.8 percent respectively. Patients with a body weight of less than 50 kg, patients > 65 years of age, and those with reduced renal function had increased bleeding and adverse event rates. Overall, there were not statistically significant differences for serious adverse events or adverse events between fondaparinux and enoxaparin. During treatment, the most frequent serious adverse event category was platelet, bleeding, and clotting disorders. However, statistically significant differences were noted for anemia and postoperative hemorrhage favoring enoxaparin.¹³

CONCLUSION: COMPARATIVE SAFETY – BLEEDING

The available evidence suggests that bleeding is more common with the use of fondaparinux than with enoxaparin.

This is particularly true in patients weighing less than 50 kg, over 65 years of age, and those with reduced renal function. Fondaparinux is specifically contraindicated in patients with severe renal impairment (creatinine clearance < 30mL/min) and in patients weighing less than 50 kg for prophylactic use.¹

COMPARATIVE SAFETY – HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

The FDA safety review of fondaparinux noted that overall thrombocytopenia was seen with similar frequency for enoxaparin and fondaparinux, 3.1 percent and 2.9 percent respectively. The rates of positive ELISA test for heparin antibodies were fondaparinux 4.3 percent and enoxaparin 3.3 percent. Serotonin release tests were performed only in ELISA positive patients. Among ELISA positive patients, the rates of positive serotonin release tests were fondaparinux 16.5 percent and enoxaparin 11.4 percent. The frequency of patients having both thrombocytopenia and a positive ELISA test was 2.9 percent for both treatment groups. Overall, the frequency of patients having both a venous thromboembolism and positive ELISA test was fondaparinux 6.7 percent and enoxaparin 9.8 percent.¹³

CONCLUSION COMPARATIVE SAFETY – HEPARIN - INDUCED THROMBOCYTOPENIA (HIT)

Fondaparinux may be associated in orthopedic surgery

studies with heparin induced thrombocytopenia (HIT) and thrombosis (HITTS), similar to unfractionated heparin and low molecular weight heparins, such as enoxaparin.¹⁴

ANTIDOTE

In the event of a serious bleeding episode occurring during treatment with an anticoagulant the availability of an antidote is an important safety consideration. Enoxaparin may be largely neutralized by one percent protamine sulfate injection.² There is no known antidote for fondaparinux injection.¹

CONTRAINDICATIONS

Fondaparinux is contraindicated in patients with severe renal impairment (creatinine clearance < 30mL/min) and for prophylactic therapy in patients weighing less than 50 kg.¹

CAUTIONS

Fondaparinux is eliminated primarily in the urine as unchanged drug. Up to 77% of a single subcutaneous dose is eliminated unchanged in the urine in 72 hours in individuals with normal kidney function. Its elimination half-life is 17-21 hours. In patients with mild renal impairment (CrCl 50-80 mL/min), the total clearance is about 25% lower. In patients with moderate renal impairment (CrCl 30-50 mL/min), clearance is approximately 40% lower. Clearance is 55% lower in

patients with severe renal impairment (<30 mL/min).

Enoxaparin is primarily metabolized in the liver. About 10% of a dose is eliminated renally as active fragments.

CONCLUSION

Fondaparinux is a synthetic activated Factor Xa inhibitor. Although not superior to enoxaparin, fondaparinux is as effective as enoxaparin in the prophylaxis of DVTs in orthopedic indications. From a safety standpoint, fondaparinux is associated with a higher rate of bleeding compared to enoxaparin. The incidence of heparin induced thrombocytopenia appears to be similar with both fondaparinux and enoxaparin. In case of overdose, enoxaparin has an antidote, while fondaparinux does not. Fondaparinux is contraindicated in patients with a creatinine clearance less than 30 mL/min and for prophylactic use in patients with body weight less than 50 kg, while enoxaparin is not.

RECOMMENDATION

Due to the higher incidence of bleeding, lack of an antidote, and contraindications based on renal function and weight, fondaparinux is not recommended as a replacement for enoxaparin in orthopedic procedures.

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THE BEERS LIST: REVISITING THE PITFALLS OF PROPOXYPHENE USE IN THE ELDERLY

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The Beers criteria were derived by expert consensus regarding safe medication use in elderly patients. The scope of these criteria includes medication that should generally be avoided in persons 65 years and older due to ineffectiveness, high risk with use, or the presence of a safer alternative.¹

Propoxyphene (Darvon) and combination products (Darvon with ASA, Darvon-N, and Darvocet-N) have been included in the Beers List as these medications offer minimal analgesic advantages over acetaminophen alone with the adverse effects of the opioid class. Use of these products has been significantly associated with the occurrence of adverse health outcomes.² In spite of consensus recommendations, propoxyphene products remain some of the most commonly prescribed drugs for the treatment of pain in elderly patients.

Although evidence-based data derived from controlled clinical trials regarding propoxyphene use in the elderly are lacking, the literature documents the potential for serious adverse effects associated with its use including accidental drug

overdose. This precipitated an announced phased withdrawal of propoxyphene products in the United Kingdom in 2005.³ Public Citizen's Health Research Group has also recently petitioned the FDA to ban all propoxyphene products in the United States. The complete petition dated February 28, 2006 may be found at <http://www.citizen.org/publications/release.cfm?ID=7420>.

The aim of this article is to briefly review the adverse effect and efficacy data of propoxyphene that has precipitated its inclusion in the Beers List and recommendation for market removal.

The cardiotoxic effects associated with propoxyphene and its major metabolite norpropoxyphene in combination with limited analgesic efficacy has been linked with a high rate of deaths attributed to accidental overdose. Cardiac toxicity accounts for up to 76 percent of deaths from propoxyphene overdose in ICU units.⁴ The norpropoxyphene metabolite is 2.5 times more potent than the parent compound in producing cardiac depression and has a half-life of 36 hours (three times longer than propoxyphene) which increases the chance of drug accumulation with increased dosing.³

The risk of accidental overdose also increases with decreased renal and hepatic function as propoxyphene and the norpropoxyphene metabolite may accumulate to toxic levels. Flanagan and colleagues have confirmed prolonged half-lives of propoxyphene

and norpropoxyphene in elderly volunteers in pharmacokinetic studies assessing single and multiple dosing regimens.⁵ The elderly may, therefore, be particularly susceptible due to decreased age-related clearance of the drug, thus, predisposing these patients to cardiotoxicity and accidental death.

The adverse cardiovascular effects that have been reported in the literature include bundle branch block, widening of the QRS complex, bradycardia, asystole, reduced myocardial contractility, and hypotension.⁴ Whitcomb and colleagues reported a case study of marked QRS complex abnormalities and sodium channel blockade in propoxyphene overdose that was reversed by lidocaine treatment.⁴ Similar results were reported by Afshari and colleagues as a dose-dependent QRS prolongation in association with propoxyphene overdose.⁶ The risk of bradycardia may be further enhanced with concomitant use of the beta-blocker metoprolol as Marraffa and colleagues recently reported a case study of metoprolol-induced bradycardia precipitated by propoxyphene-acetaminophen (Darvocet) use.⁷ Although inhibition of metoprolol metabolism by propoxyphene via the CYP2D6 system was noted as the likely culprit, it underscores the potential for additive cardiac depression in users of these medications.

Propoxyphene has also shown central nervous system toxicity in association with accumulation of the

norpropoxyphene metabolite. Dizziness induced by the drug has been associated with an increased risk of hip fractures from falls in elderly patients.⁸ In addition, the potential for increased accumulation of the drug in elderly patients heightens the risk of CNS depression and respiratory depression, adverse effects seen with other opioid analgesics. Therapeutic alternatives for treating pain in the elderly should be initially considered because tolerance, psychological dependence, and physical dependence may develop with propoxyphene use.³ Case reports of withdrawal syndrome have also been documented with propoxyphene use.⁹

Some of the most compelling evidence further elucidating the risk to benefit ratio of propoxyphene use is the documented limited analgesic efficacy of the drug. A previous review of the literature in the early 1970s by Miller and colleagues revealed that propoxyphene was no more effective than aspirin or codeine in treating pain.¹⁰ A meta-analysis by Li Wan Po and Zhang published in 1997 revealed no difference in analgesic effectiveness between acetaminophen and propoxyphene-acetaminophen.¹¹ In addition, a more recent review of randomized clinical trials by Collins and colleagues suggests that ibuprofen is more effective for most kinds of pain than propoxyphene-acetaminophen.³

The evidence reported in the literature supports an increased risk to benefit ratio associated with the

use of propoxyphene as compared with other initial therapeutic alternatives in the treatment of moderately severe pain. The risk of toxic adverse effects is inherently increased in the elderly due to age-related decreases in renal function delaying clearance of the drug and promoting accumulation with typical dosing schedules (taken up to six times per day). The specific findings discussed here should lend credence in discouraging clinicians from prescribing propoxyphene products for elderly patients if at all possible. The potential for placing the patient at risk for harm appears to greatly outweigh the analgesic benefits of propoxyphene products. It is within this context of addressing safety concerns and ensuring optimal therapeutic outcomes for the elderly that the Beers criteria were initially developed.

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COMMENTARY - PATIENT COUNSELING: ARE PHARMACISTS SENDING THE WRONG MESSAGE?

Disheartening results from a survey done by Accenture Health & Life Sciences released on April 10, 2006 indicated that U.S. prescription drug consumers trust the Internet almost as much as they do pharmacists as a source for drug information. More than 60 percent of the survey's 1,000 respondents said that physicians are their most trusted drug information source, followed by pharmacists and Internet medical sites, 16 percent and 13 percent, respectively. Eighty-one percent of the respondents said that questions about drug safety are the main reason they conduct more research today than they did five years ago.¹

Over the past 15 years the Food and Drug Administration's (FDA) Division of Drug Marketing, Advertising and Communications (DDMAC) has conducted its own consumer surveys that in certain respects support the results of the Accenture survey that the public's main questions about prescription drugs concern their safety.

A DDMAC survey of consumers' behaviors and attitudes about direct-to-consumer (DTC) advertising released in November 2004 suggested that DTC advertisements prompted a sizable percentage of consumers to seek additional information about a drug. The number of consumers searching the Internet for drug or health information jumped considerably—from 18 percent in 1999 to 38 percent in 2002—with information about risks being most commonly sought. Far more consumers looked for information about adverse effects than about benefits (61% vs. 10%).²

An earlier survey, conducted by DDMAC in 1999, found that 59 percent of consumers surveyed indicated that they strongly or somewhat strongly agreed that DTC ads do not contain enough information about the possible risks and negative effects of using a drug.³

National telephone surveys conducted by the FDA in 1992, 1994, 1996, and 1998 found that less than 40 percent of physicians provided their patients with any information about precautions and adverse drug effects. Pharmacists scored even lower, less than 30

percent of pharmacists communicated any precaution or adverse drug effect information to consumers.⁴

Is it possible that pharmacists are being bypassed by a public seeking a specific type of information – risk information about the drugs they are being prescribed? This raises issues about the availability and quality of drug information, including drug risk information, provided by pharmacists.

The economics of pharmacy make it difficult for pharmacists to fulfill the drug information role that consumers are seeking. Pharmacists make money when they are filling prescriptions not when they are counseling patients. If a pharmacist does counsel on a drug's risks, the consumer may refuse the drug and no sale. This, of course, is the right of a fully informed consumer but it is an economic negative under the present system.

Two large surveys have questioned the quality of written drug information, including drug safety information, distributed in pharmacies to prescription drug consumers.^{5,6} In addition, a report published in the April 3, 2006 issue of *Drug Topics* suggests that pharmacists may not be distributing FDA mandated drug safety information in the form of Medication Guides.

Anecdotally, pharmacists' counseling may emphasize medication compliance with prescribers' orders rather than

issues of a drug's safety. In such a scenario could the pharmacist be viewed simply by consumers as just another cog in the drug selling machine and prompting consumers go elsewhere for the information they want? The public is ingenious in finding answers to their questions no matter if the answers are credible or even useful.

Are there solutions to pharmacists being bypassed as a source of drug information? Nothing seems to be in happening in the U.S. However, legislation recently introduced in the Parliament of the Canadian province of Ontario recognizes the valuable role pharmacists play in patient care by paying them to provide enhanced patient counseling about the appropriate use of medications.⁷

Of course, the system of financing healthcare is different in Canada than in the U.S. Perhaps U.S. pharmacists should be looking north for ideas on how to become a more integrated part of primary care and how to get reimbursed for patient counseling.

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