Evaluation of a protocol-based intervention to promote timely switching from intravenous to oral paracetamol for post-operative pain management: an interrupted time series analysis

Sabry, N. , Dawoud, D. , Alansary, A. , Hounsome, N. and Baines, D.

Original citation & hyperlink:
Sabry, N. , Dawoud, D. , Alansary, A. , Hounsome, N. and Baines, D. (2015) Evaluation of a protocol-based intervention to promote timely switching from intravenous to oral paracetamol for post-operative pain management: an interrupted time series analysis. Journal of Evaluation in Clinical Practice, volume 21 (6): 1081-1088
http://dx.doi.org/10.1111/jep.12463

DOI 10.1111/jep.12463
ISSN 1365-2753
ESSN 1365-2753

Publisher: Wiley

This is an Accepted Manuscript of an article published by Taylor & Francis in Journal of Evaluation in Clinical Practice on 22nd October 2015, available online: http://www.tandfonline.com/10.1111/jep.12463

Manuscript

Abstract

Rationale, aims and objectives: Timely switching from intravenous to oral therapy ensures optimised treatment and efficient use of healthcare resources. Intravenous (IV) paracetamol is widely used for postoperative pain management but not always switched to the oral form in a timely manner, leading to unnecessary increase in expenditure. This study aims to evaluate the impact of a multifaceted intervention to promote timely switching from the IV to oral form in the postoperative setting.

Methods: An evidence-based prescribing protocol was designed and implemented by the clinical pharmacy team in a single district general hospital in Egypt. The protocol specified the criteria for appropriate prescribing of IV paracetamol. Physicians were provided with information and educational sessions prior to implementation. A prospective, quasi-experimental study was undertaken to evaluate its impact on IV paracetamol utilisation and costs. Data on monthly utilisation and costs were recorded for 12 months before and after implementation (January 2012 to December 2013). Data were analysed using interrupted time series analysis.

Results: Prior to implementation, in 2012, total spending on IV paracetamol was 674,154.00 Egyptian Pounds (L.E.) ($236,68.00). There was a non-significant ($p>0.05$) downward trend in utilisation (-32 ampoules/month) and costs (reduction of 632 L.E. ($222)/month). Following implementation, immediate decrease in utilisation and costs ($p<0.05$) and a trend change over the follow-up period were observed. Average monthly reduction was 26% (95% CI: -24% to -28%, $p <0.001$).

Conclusion: A multifaceted, protocol-based intervention to ensure timely switching from IV-to-oral paracetamol achieved significant reduction in utilisation and cost of IV paracetamol in the first five months of its implementation.

Introduction

In the current health care spending landscape, where demand is increasing and resources are limited, it is essential that hospitals implement evidence-based policies for the utilisation of drugs[1]. The choice of the appropriate route of administration and dosage form is an important step in the prescribing of medicines to achieve optimised outcomes from the limited drugs' budget [2,3]. Given the differential pricing of the medicines' formulations, it is important that the choice between these is guided by evidence regarding cost-effectiveness. For example, in the context of operative and intensive care, the choice of the intravenous route when the oral route is possible or a nasogastric tube is being used would not be appropriate [4].

Hospitalised patients often begin to receive their medications intravenously when acutely ill or postoperatively. However, they are not usually switched to the oral medication in a timely manner (i.e. when they become stable and start taking oral medications or diet)[5]. Clinical guidelines on acute pain management in adults in the USA,France, the United Kingdom and Australia recommend oral administration of drugs as soon as patients can take them [6-9]. Hence, interventions have been developed and implemented to ensure timely switching from the intravenous to the oral route in the post-operative administration of drugs. For example, Colombet et al. implemented an intervention to promote early switching from IV to oral proton pump inhibitors (PPIs) following a sharp increase in the utilisation and associated costs of IV forms of PPIs. The intervention was successful in reducing the utilisation of IV PPIs, although in the long run this change was not sustainable [8]. Ripouteau et al. applied a multifaceted intervention to promote early switching from IV to oral administration of paracetamol for pain management [7]. The authors argued that patients, nurses and other

health care professionals erroneously believed that IV paracetamol was more effective and were not aware of the much higher costs associated with its use.

Acetaminophen (paracetamol or N-acetyl-P-aminophenol [APAP]) is a well-known and approved medication for the management of mild to moderate perioperative pain alone; the management of moderate to severe pain with adjunctive opioid medication; and reduction of fever [11]. It has been suggested that, its mechanism of action is produced through central effect. The analgesic effect targets cyclooxygenase isoenzymes, endogenous opioid or serotoninergic bulbospina pathways and/or cannabinoid tone [12]. The antipyretic effect is mediated through inhibition of prostaglandin formation that otherwise acts to increase the temperature within the hypothalamus [13].

The safety, tolerability and non-sedating effect of paracetamol have been considered the main advantages of this medication, although how safe paracetamol is has been recently disputed [14]. It is available in the market as oral, rectal and IV preparations. The IV preparation (10 mg/ml solution for infusion) has been available to the European market since 2002 and was introduced to the Egyptian market in 2006 following approval from the Egyptian Ministry of Health. In 2010 it was marketed in the USA. Oral paracetamol is a simple well-tolerated analgesic; but if meaningful early plasma concentrations are required, a more generous loading dose is needed [15].The IV form is successful in achieving rapid therapeutic concentrations that can subsequently be maintained by oral absorption [16,17]. There is a considerable difference between the price of the IV and the oral forms in the Egyptian market, with the oral form priced at 0.05 L.E. ($0.02) per 100 mg while the IV form priced at 1.95 L.E. ($6.85) per 100 mg for the IV form.

Oral dosage forms have several advantages compared to IV, including: lower cost, less administration time by nursing staff with lower risk of infection, and increased patient comfort and safety through eliminating the requirement for intravenous catheters [18]. Prior research in the setting of community-acquired pneumonia has demonstrated that an early IV-

to- Per Oral (PO) switch of medications can also shorten the duration of hospitalisation [19,20].

In Egyptian hospitals the absence of electronic drug-ordering systems - which would enable a central computer to provide a daily list of all patients who are on IV paracetamol for long periods (and are therefore potential candidates for an IV-to-PO switch) - greatly reduces the number of patients who are switched in a timely manner. Given the large difference in price between oral and IV forms, this represents a considerable waste in a health system that is already struggling to provide basic health care due to its limited resources.

Ripouteau and colleagues proposed the use of an educational intervention targeted at nurses and other health care professionals to promote early switching from IV to oral paracetamol which showed promising results. However the study was conducted in France in 2000 and its results would be of limited generalisability to Egyptian hospitals aiming to achieve this [7]. Hence, we developed a multifaceted, protocol-based intervention to increase the efficiency of postoperative pain management by identifying patients who are suitable candidates for IV-to-PO switching and promptly implementing the switch. The aims of this pilot study were: to assess the impact of this multifaceted, protocol-based intervention on the utilisation and cost of IV paracetamol and to assess the feasibility of the protocol implementation and its acceptability among physicians, with the aim of generating evidence to inform national guideline development and implementation. In contrast to Ripouteau et al, our intervention was primarily restrictive and was implemented as a pharmacist-led initiative at a whole hospital level, rather than a single surgical department [7].

Methods

This is a prospective, quasi-experimental study; where data were collected before and after the implementation of this non-computerised protocol. The effect of this protocol on the utilisation and costs of IV paracetamol was assessed using interrupted time series analysis.

1. Setting

The intervention was implemented in a single district general hospital in the Egyptian capital, Cairo. The hospital, which has140 beds, is covered by 22 specialties. The average number of surgeries per month is around 400, performed by 17 of the 22 specialties.

2. Standard procedures for pain management prior to the intervention:

The standard procedure for postoperative pain management in the hospital was to use IV paracetamol immediately after surgery and to maintain it as long as the patient reported feeling pain or until discharge. Ideally, patients would then be switched to oral paracetamol when they are able to take oral medications. However, this was not usually done in a timely manner.

3. Intervention design and implementation:

The general approach was to develop, implement and assess the impact of the intervention. The drugs and therapeutics committee (DTC) oversaw the approval, development and implementation of the protocol. The process involved the following stages:

3.1. Defining the criteria for IV paracetamol prescribing:

In accordance with the nature of the hospital, a general hospital with multispecialty, it was necessary to tailor a list suitable to the nature of the hospital patients. This list was developed based on published guidelines [8,9] and specified that IV paracetamol can be prescribed:

- for surgical patients within 48 hours post-operatively;
- for null-per-oral (NPO) patients or patients with mucositis suffering from pain;
- for other pain patients only after the approval of the DTC chairman or the pain management team;
- in acutely febrile patients (temperature > 38°C), where one single dose of IV paracetamol is recommended, followed by oral form if a regular regimen is required; and
- to patient with erratic gastric absorptions.

3.2. Designing the IV-to-PO switching protocol

The main steps of the protocol are summarised in Figure 1 which illustrates the steps involved in the process.

Figure 1: Flow chart illustrating the steps involved in the protocol-based process and the criteria for dispensing IV paracetamol

3.3. Revision and approval of the protocol

The protocol was presented to both the pain management team and the DTC for revision and approval to ensure local consensus and physician buy-in.

3.4. Pharmacists training

All the ward pharmacists in the hospital received written orientation about the inclusion criteria and on-the-job training on the implementation of the protocol.

3.5. Physician orientation

A 10-minute session was designed to be delivered to the physicians. These sessions were delivered by the pharmacy team. Also, electronic messages (via E-mails and SMS) were sent to all the physicians via the hospital medical council to inform them about the new protocol and the date it was due to come into effect.

3.6. Official implementation of the protocol

The approved protocol was officially launched on the 1st of January 2013. From this date, all the medication sheets were screened by the ward pharmacists twice daily before dispensing doses (10 am dose and 10 pm dose) to ensure that the policy was being implemented.

4. Data collection and analysis

In order to assess the change in the utilisation of IV paracetamol, data on the number of IV ampoules consumed for the whole hospital were extracted from the hospital pharmacy records on a monthly basis over one year, from the 1st January 2013 to 31st December 2013. Data for the pre-implementation phase were also extracted from the hospital pharmacy's dispensing records for an equivalent period of time directly preceding the implementation of the intervention (1st January 2012 to 31st December 2012). Further to reviewers' comments, data on the consumption and costs of oral paracetamol were also obtained from the pharmacy records and analysed similarly. As the intervention was not targeted at individual patients and no patient identifiable data were collected, patient consent was not required.

Costs of IV paracetamol were calculated by multiplying the number of dispensed ampoules by their unit cost (19.50 L.E. ($6.85). Similarly, the costs of oral paracetamol were calculated using its unit cost (0.05 L.E. ($0.02) per 100 mg).

Paired sample t-test was used to assess the significance of the change in monthly utilisation and costs before and after the intervention. Statistical significance was set at $p < 0.05$. The time series (12 points before and 12 points after the intervention implementation) was analysed using Interrupted Time Series (ITS) analysis. Autoregressive Integrated Moving Average (ARIMA) models were used to analyse associations between observations in the pre-intervention series [21,22]. The outcome of this analysis satisfied the assumptions of the general linear regression model; hence, a segmented regression model including time and intervention terms could be applied to the original time series.

All the analysis was conducted using SPSS (v.16) software. Costs were calculated in 2012-2013 Egyptian Pounds (L.E) and converted to US Dollars using the International Monetary Fund (IMF) Purchasing Power Parity (PPP) (using CCEMG – EPPI-Centre Cost Converter available at: http://eppi.ioe.ac.uk/costconversion/Default.aspx) .

Results

Monthly and total annual inpatient utilisation and costs of IV paracetamol in the period from January 2012 to December 2013 and the change in monthly and annual costs are presented in Table 1.

Table 1: Total monthly IV paracetamol utilisation and associated costs over the study period (January 2012 to December 2013)

Overall, the total annual utilisation of IV paracetamol was 34,572 ampoules in 2012, before the introduction of the intervention. The average monthly utilisation was 2,881 ampoules (95% CI: 2,807-2,955). This equates to a total cost of 674,154.00 L.E., with an average monthly cost of 56,180.00 L.E. (95% CI: 54,739.00 to 57,620.00 L.E.).

In 2013, following implementation, the total utilisation of IV paracetamol fell to 25,344 ampoules with a monthly average of 2,111 (95% CI: 2068 to 2155). The total cost in 2013 was 494,013.00 L.E. with a monthly average of 41,168.00 L.E. (95% CI: 40,317.00 to 42,018.00 L.E.).

Thus, the reduction in monthly utilisation compared to pre-intervention values ranged from 329 to 1,234 ampoules with an average of 770 ampoules (95% CI: 677 to 830). This reduction was highly statistically significant ($p < 0.001$). The monthly saving achieved, Figure 2, ranged from 6,416.00 to 24,063.00 L.E., with an average monthly saving of 15,012.00 L.E. (95% CI: 13,599.00 to 16,464.00 L.E., $p < 0.001$). These data showed that the relative reduction in monthly utilisation and costs ranged from 14% to 39% with an average of 26% (95% CI: 24% to 28%, $p < 0.001$).

Using the Interrupted Time Series analysis, to adjust for the level of change observed in the pre-intervention period, it was estimated that before the intervention there was a downward trend with a decrease of 32 units per month; however, this was not statistically significant ($p = 0.056$) (Table 2). Similarly, there was an average decrease in monthly cost by 632 L.E.($222), which was not statistically significant ($p = 0.067$) (Table 2). After the implementation of the intervention, in January 2013, there was an immediate change in the average monthly utilisation and costs and a trend change was observed over the whole follow up period.

In the first month, upon the introduction of the intervention, there was a statistically significant reduction in utilisation ($p = 0.001$) and costs ($p = 0.003$) compared with the pre-intervention period. The initial effect of the intervention decreased with time (months 1 to 5). After month 5, the reduction was still evident in absolute and relative terms but not significantly different in statistical terms from the pre-intervention period for both monthly

utilisation (p = 0.07) and costs (p = 0.071). This suggests that the intervention effect was sustained for the first 5 months of implementation but its effect was attenuated after this period. Figure 2 shows the time series for IV paracetamol utilisation before and after the implementation of the intervention.

Table 2: Summary of the AutoRegressive Integrated Moving Average (ARIMA) model analysis showing the estimated reduction in IV paracetamol utilisation and costs following intervention implementation compared with pre-intervention levels.

Figure 2: Time series of monthly IV paracetamol utilisation before and after the implementation of the protocol-based intervention.

The consumption of oral paracetamol and associated costs were significantly higher in 2013 compared to 2012 (p=0.84, see Table 3). ARIMA analyses showed that there was an increase in the consumption of the oral form in the first months upon the introduction of the intervention, however, this increase was not statistically significant.

Table 3: Total monthly oral paracetamol utilisation over the study period (January 2012 to December 2013)

To assess the net effect of the intervention, the total cost of both the oral and IV forms was also analysed. This has confirmed that there was a significant reduction in total paracetamol costs in the first 5 months of 2013 ($p < 0.05$), driven by the reduction in the consumption and cost of the more expensive IV form.

The total number of admissions to the hospital was 10,682 in 2012 (before the introduction of the intervention) and 10,982 in 2013 (following the introduction of the intervention). The average monthly number of admissions was 890 (SD = 53) in 2012 and 915 (SD = 55) in

2013. The difference in the mean number of admissions between the two years was not statistically significant ($p = 0.27$).

Discussion

The results of this study showed that, a multifaceted, protocol-based intervention implemented at a general hospital achieved a significant reduction in the utilisation and cost of IV paracetamol. The effect was statistically significant, showing a significant discontinuity in the utilisation and costs of IV paracetamol immediately after its implementation and a sustained effect for the first 5 months. In absolute terms, this reduction continued over the study period. Adjusting for the pre-intervention trend showed that after 5 months the change in the rate of reduction in utilisation was not statistically significant compared with the pre-intervention trend.

Pain management in hospitalised patients is a necessary skill set for all physicians. Pain is so pervasive in the hospital setting that it is sometimes referred to as "the fifth vital sign," and failure to manage pain has important implications not only for physicians, but also for the hospitals where they practice [23]. The World Health Organization (WHO) reports that the irrational use of medicines is a major problem worldwide [24]. The over-use of parenteral formulations, while oral formulations would be as appropriate, is one of the key factors contributing to the irrational use of medicines and unnecessary increase in drug spending [25]. IV-to-PO switching within an appropriate time postoperatively is one of the major areas that could be targeted to rationalise the use of parenteral forms [26]. Thus, the results of this study have relevance internationally to help ease the burden on already stretched resources.

The cost of IV paracetamol is several times higher compared to the oral form (0.05 L.E. ($0.02) per 100 mg for the oral vs 1.95 L.E. ($6.85) per 100 mg for the IV preparation), this would not stop physicians from prescribing the IV formulation in Egypt. However, adherence

to guidelines regarding early switching from IV to oral therapy in Egypt is still not appropriate. The lack of computerised prescribing systems is a major contributing factor to this low level of adherence [27]. However, this poor adherence is a problem also in other developed countries (e.g. the United Kingdom) [28].

In the context of postoperative pain management, the use of the IV route is clinically justified where there is an urgent need to treat pain and/or when other routes of administration are not possible [29]. However, the IV route may not always be used appropriately and can be associated with potential problems such as: associated risks of infection; local pain and inflammation; possible overdose with concomitant oral medicines containing paracetamol, especially in patients with hepatic impairment or severe renal impairment; failure to adjust the dose according to body weight or other patient-related factors. These issues may lead to a considerable increase in nursing time and costs [7,29]. Hence, the recommendation is to switch to the oral route as soon as this becomes possible. Adhering to this evidence-based prescribing practice has proven to be cost-effective; achieving positive outcomes in terms of reduced risk of infection and hospital length of stay while reducing the costs associated with IV paracetamol use [7]. The effect of such adherence was evident in this intervention study as well, where a significant reduction in utilisation and costs was achievable without adversely affecting the level of postoperative pain management, where patient-requested analgesics' utilisation levels remained stable over the two-year study period. The utilisation of oral paracetamol increased in the first months upon the introduction of the intervention, however this increase was not statistically significant. The total cost of paracetamol (oral plus IV) showed a significant reduction in the first 5 months, driven by the reduction in the utilisation of more expensive IV form.

Previous studies that examined the effectiveness of interventions to promote IV- to Oral switching for paracetamol, PPIs and antibiotics have shown similar results, with an initially significant change in physicians' prescribing behavior, which tended to level off [7,10,30,31]. A systematic review of the effectiveness of similar interventions to improve antibiotic prescribing in hospitals included studies of interventions directed to changing the route of administration [32]. The review concluded that restrictive interventions, such as automatic stop orders similar to the intervention used in this study, had a significantly greater impact on prescribing outcomes in the short-run (6 months) but not in the long-run (12 and 24 months) when compared to persuasive interventions [32]. This trend suggests that there may be a need for follow-up measures and continuous education to maintain the achieved change. However, overall, the average level of change seen in this study (26% reduction in utilisation of IV paracetamol) was found to be within the range reported in this Cochrane review when using primarily restrictive interventions (17% to 34% in the desired direction) [32]. It is also likely that the level of utilisation may have reached an optimum level, with no further room for improvement.

The use of ITS analysis can be a particularly useful method in prescribing research to allow the analysis of drug prescribing and utilisation levels and trends. It can be a powerful tool for hospital pharmacies to track and identify challenging and non-evidence based prescribing practices that require remedial action. It has been used to assess the effectiveness of interventions to improve prescribing of various medications including antidepressants, antibiotics and proton pump inhibitors [10,33,34]. The implementation of a computer physician order entry (CPOE) system can further enhance the usability of this method and simplify the data collection. A CPOE system would also make it possible to design interventions based on sending computerised reminders to prescribers in addition to facilitating the collection of real-time data for audit and research purposes [18].

There are a number of limitations to our study. Firstly, it was conducted at a single hospital in a large city and consequently the findings may not be generalisable to other settings. Secondly, the study focused on assessing changes in process measures on a whole hospital level rather than clinical outcomes on an individual patient level. Finally, the results may have been confounded by other factors such as the case mix; given the quasi-experimental before-and-after research design. Nevertheless, and despite these limitations, the study showed that this protocol-based intervention has achieved considerable efficiency saving in a resource-limited setting. Reinforcing the messages delivered through the implementation activities on a bi-annual basis can further improve the outcomes and ensure maintenance of a positive effect. Further research should focus on assessing patient-level, clinical outcomes as part of a full pharmacoeconomic evaluation to assess the cost effectiveness of this intervention.

In conclusion, the implementation of a protocol-based intervention to achieve a timely switch from IV to oral paracetamol in the context of postoperative pain management achieved an immediate significant reduction in the utilisation and cost of IV paracetamol. However, as with other interventions aimed at changing prescribing behaviour, this effect may require additional measures to be sustainable. Choosing the appropriate administration route is an important step in the prescribing process that can optimise patient outcomes in a cost-effective manner.

Acknowledgement

The authors would like to acknowledge Dr Barry Hounsome for his efforts in critically reviewing and proof-reading the manuscript. We are also indebted to the clinical pharmacy team and the inpatient pharmacy staff for their role in implementing the protocol.

Author contributions

NS and AA were involved in the conception and design of the study and oversaw data collection. DD, NH and DB contributed to the design of the study and advised on data collection. DD and NH undertook the data analysis. DD drafted the manuscript. NS, AA, NH and DB provided comments and critically revised the manuscript. All authors approved the final manuscript.

References:

1. Picton, C. and Wright, H. (2013) Medicines Optimisation: Helping patients to make the most of medicines. Good practice guidance for healthcare professionals in England. London, Royal Pharmaceutical Society of Great Britain (RPSGB).

2. deVries, T., Henning, R., Hogerzeil, H., Fresle, D. (1995) Guide to good prescribing: A practical manual. Geneva, World Health Organization Action Programme on Essential Drugs.

3. Larkin, M. (2001) Evidence-based prescribing made simple. *Lancet*, 357(9254), 448.

4. Fenlon, S., Collyer, J., Giles, J., Bidd, H., Lees, M., Nicholson, J., Dulai, R., Hankins, M., Edelman, N. (2013) Oral vs intravenous acetaminophen for lower third molar extractions under general anaesthesia: is oral administration inferior? *British Journal of Anaesthesia*, 110(3), 432-437. Doi: 10.1093/bja/aes387

5. Cunha, B. (2001) Intravenous to oral antibiotic switch therapy. *Drugs Today (Barc),* 37(5), 311-319.

6. Carr, D., Jacox, A., Chapman, C. (1992) Acute pain management in adults: operative procedures. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, US Department of Health and Human Services (Quick reference guide for clinicians No 1. AHCPR Publication No 92-0019.)

7. Ripouteau, C., Conort, O., Lamas, J.P., Auleley, G.R., Hazebroucq, G., Durieux, P. (2000) Effect of multifaceted intervention promoting early switch from intravenous to oral acetaminophen for postoperative pain: controlled, prospective, before and after study. *British Medical Journal*, 321, 1460-1463. Doi: http://dx.doi.org/10.1136/bmj.321.7274.1460

8. Western Australian Therapeutic Advisory Group. (2012) Guidance for the use of intravenous paracetamol in WA public hospitals, WA.TAG advisory note. http://www.watag.org.au/watag/docs/IV_paracetamol_Advisory_Note_26Nov12.pdf. (accessed 26 August 2015)
9. The Royal Bournemouth and Christchurch Hospital, NHS Foundation Trust. (2012) Guideline for paracetamol use. http://www.dorsetccg.nhs.uk/Downloads/aboutus/medicines-management/Other%20Guidelines/Guideline%20for%20paracetamol%20use%20RBCH.pdf. (accessed 26 August 2015)
10. Colombet, I., Sabatier, B., Gillaizeau, F., Prognon, P., Begue, D., Durieux, P. (2009) Long-term effects of a multifaceted intervention to encourage the choice of the oral route for proton pump inhibitors: an interrupted time-series analysis. *Quality and Safety in Health Care,* 18, 232–235. Doi:10.1136/qshc.2007.023887
11. Pasero, C., Stannard, D. (2012) The role of intravenous acetaminophen in acute pain management: a case-illustrated review. *Pain Management Nursing,* 13(2),107-24.
12. Mattia, A., Coluzzi, F. (2009) What anesthiologists should know about paracetamol (acetaminophen). *Minerva Anestesiology,* 75(11), 644-653.
13. Graham, G., Scott, K. (2005) Mechanism of action of paracteamol. *American Journal of Therapeutics,* 12(1), 46-55.
14. Joshi, G.P. (2005) Multimodal analgesia techniques and postoperative rehabilitation. *Anesthesiology Clinics of North America,* 23(1), 185-202. Doi:10.1016/j.atc.2004.11.010
15. Holmer-Pettersson, P., Owall, A., Jakobsson, J. (2004) Early bioavailability of paracetamol after oral or intravenous administration. *Acta Anaesthesiologica Scandinavica,* 48, 867-70. DOI: 10.1111/j.0001-5172.2004.00452.x

16. Macario, A. and Royal, MA. (2011) A literature review of randomized clinical trials of intravenous acetaminophen (paracetamol) for acute postoperative pain. *Pain Practice,* 11, 290–610. Doi: 10.1111/j.1533-2500.2010.00426.x.
17. Moller, P., Sindet-Pedersen, S., Petersen, C.T., Juhl, G.I., Dillenschneider, A., Skoglund, L.A. (2004) Onset of acetaminophen analgesia: Comparison of oral and intravenous routes after third molar surgery. *British Journal of Anesthesia*; 94, 642-648. Doi: 10.1093/bja/aei109
18. Fischer, M., Solomon, D., Teich, J., Avorn, J. (2003) Conversion from intravenous to oral medications: Assessment of a computerized intervention for hospitalized patients. *Archives of Internal Medicine,* 163(21), 2585-2589. Doi:10.1001/archinte.163.21.2585.
19. Ramirez, J., Vargas, S., Ritter, G.W., Brier, M.E., Wright, A., Smith, S., Newman, D., Burke, J., Mushtaq, M., Huang, A. (1999) Early switch from intravenous to oral antibiotics and early hospital discharge. *Archives of Internal Medicine,* 159, 2449-2454. doi:10.1001/archinte.159.20.2449
20. Oosterheert, J.J., Bonten, M.J., Schneider, M.M. et al. (2006) Effectiveness of early switch from intravenous to oral antibiotics in severe community acquired pneumonia: multicentre randomised trial. *British Medical Journal*, 333, 1193-1205. Doi: http://dx.doi.org/10.1136/bmj.38993.560984.BE
21. Box, G.E.P., Jenkins, G.M. (1976) Time series analysis, forecasting and control. San Francisco: Holden Day.
22. Greene, W.H. (2002) Econometric analysis. 5th ed. Englewood Cliffs: Prentice-Hall.
23. Harrington, D. (2013) IV Acetaminophen: The Hospitalist's Perspective. Today's Hospitalist Special Report.

http://www.todayshospitalist.com/index.php?b=articles_read&cnt=1637. (accessed 14 June 2015)

24. World Health Organization (WHO). (2012) The pursuit of responsible use of medicines: Sharing and learning from country experiences. http://www.who.int/medicines/publications/responsible_use/en/ (accessed 14 June 2015)
25. Lau, B., Pinto, B., Thiemann, D., Lehmann, C. (2011) Budget impact analysis of conversion from intravenous to oral medication when clinically eligible for oral intake. *Clinical Therapeutics,* 33(11), 1792 –1796. Doi:10.1016/j.clinthera.2011.09.030
26. Cyriac, J. and James, E. (2014) Switch over from intravenous to oral therapy: A concise overview. *Journal of Pharmacology and Pharmacotherapy,* 5(2), 83-87. DOI: http://dx.doi.org/10.4103/0976-500X.130042
27. O'Neal, J. (2013) The utility of intravenous acetaminophen in the perioperative period. *Frontiers in Public Health,* 1, 25. Doi: 10.3389/fpubh.2013.00025
28. Marsden, M. (2010) Auditing use of IV paracetamol in a surgical division and intensive care. *Clinical Pharmacist*, 2, 225-228.
29. Tzortzopoulou, A., McNicol, E.D., Cepeda, M.S., Francia, M.B.D, Farhat, T., Schumann, R. (2011) Single doses of intravenous formulations of paracetamol (acetaminophen) to reduce pain after surgery in adults and children. *Cochrane Database of Systematic Reviews,* 10. DOI: 10.1002/14651858.CD007126.pub2
30. Rhew, D.C., Tu, G.S., Ofman, J., Henning, J.M., Richards, M.S., Weingarten, S.R. (2001) Early switch and early discharge strategies in patients with community-acquired pneumonia: a meta-analysis. *Archives in Internal Medicine,* 161(5),722-727. doi:10.1001/archinte.161.5.722

31. McLaughlin, C.M., Bodasing, N., Boyter, A.C., Fenelon, C., Fox, J.G., Seaton, R.A. (2005) Pharmacy-implemented guidelines on switching from intravenous to oral antibiotics: an intervention study. *Quarterly Journal of Medicine*, 98 (10), 745–52. DOI: http://dx.doi.org/10.1093/qjmed/hci114

32. Davey, P., Brown, F., Fenelon, L. et al. (2013) Interventions to improve antibiotic practices for hospital inpatients. *Cochrane Database of Systematic Reviews*, 4. DOI: 10.1002/14651858.CD003543.pub2

33. Hanbury, A., Farley, K., Carl, Thompson., Wilson, P., Chambers, D., Holmes, H. (2013) Immediate versus sustained effects: interrupted time series analysis of a tailored intervention. *Implementation Science*, 8,130. Doi:10.1186/1748-5908-8-130

34. Ansari, F., Gray, K., Nathwani, D., Phillips, G., Ogston, S., Ramsay, C., Davey, P. (2003) Outcomes of an intervention to improve hospital antibiotic prescribing: interrupted time series with segmented regression analysis. *Journal of Antimicrobial Chemotherapy*, 52, 842–848. Doi: 10.1093/jac/dkg459

Figure legends:

Figure 1: Flow chart illustrating the steps involved in the protocol-based process and the criteria for dispensing IV paracetamol

Figure 2: Time series of monthly IV paracetamol utilisation before and after the implementation of the protocol-based intervention.

Tables

Table 1: Total monthly IV paracetamol utilisation and associated costs over the study period (January 2012 to December 2013)

Month	Units (1000 mg single use ampoule)		Costs (L.E.)*		
	2012	2013	2012 (a)	2013 (b)	Difference in cost (b-a)
January	2996	2045	58,422	39,878	-18,544
February	2605	1994	50,798	38,883	-11,915
March	3073	2149	59,924	41,906	-18,018
April	3067	2128	59,807	41,496	-18,311
May	2986	2005	58,227	39,098	-19,129
June	3248	2305	63,336	44,948	-18,388
July	3152	1918	61,464	37,401	-24,063
August	2752	2301	53,664	44,870	-8,794
September	2925	2345	57,038	45,728	-11,310
October	2428	2099	47,346	40,931	-6,415
November	2839	2179	55,361	42,491	-12,870
December	2501	1866	48,770	36,387	-12,383
Total	**34572**	**25344**	**674,154**	**494,013**	**-180,141**

***** *IV paracetamol unit cost = 19.5 L.E.*

Table 2: Summary of the AutoRegressive Integrated Moving Average (ARIMA) model analysis showing the estimated reduction in IV paracetamol utilisation and costs following intervention implementation compared with pre-intervention levels.

Time after introducing intervention (months)	Change in utilisation (units)		Change in cost (L.E.)	
	Mean (95% CI)	P-value	Mean (95% CI)	P-value
0 (pre-intervention)	-32 (-66, 2)	0.056	-6,32(-1,342, 78)	0.067
1	-636 (-985, -287)	0.001*	-11,418 (-18,575, -4,261)	0.003*
2	-585(-938, -233)	0.002*	-10,695 (-1,7966, -3,424	0.005*
3	-534 (-897, -171)	0.005*	-9,972 (-1,7489, -2,455)	0.009*
4	-484 (-864, -103)	0.013*	-9,248 (-17,127, -1,369)	0.019*
5	-433 (-836, -29)	0.031*	-8,525 (-16,870, -180)	0.038*
6	-382 (-813, 49)	0.070	-7,802 (-16,700, 1,096)	0.071
7	-331(-794, 132)	0.137	-7,079 (-16,603, 2,445)	0.122
8	-280 (-778, 218)	0.237	-6,355 (-16,561, 3,851)	0.191
9	-229(-765, 307)	0.364	-5,632 (-16,570, 5,306)	0.276
10	-178 (-754, 398)	0.509	-4,909 (-16,616, 6,798)	0.372
11	-127 (-744, 490)	0.659	-4,186 (-16,695, 8,323)	0.475
12	-76(-736, 584)	0.804	-3,463 (-16,802, 9,876)	0.578

**Statistically significant (P < 0.05)*

Table 3: Total monthly oral paracetamol utilisation over the study period (January 2012 to December 2013)

Month	2012 (a)	2013 (b)	Change in utilisation (b-a)	Change in costs (L.E)*
January	3901	6222	2321	580
February	3797	6193	2396	599
March	3950	5226	1276	319
April	3449	3680	231	58
May	4312	4261	-51	-13
June	3007	3991	984	246
July	3475	2763	-712	-178
August	2459	2875	416	104
September	3499	4135	636	159
October	3547	3593	46	12
November	4250	3856	-394	-99
December	4737	4025	-712	-178
Total	**44383**	**50820**	**6437**	**1,609**

**calculated using unit cost of 0.25 L.E/500 mg.*