BIOPHARMACY

TAPENTADOL AND TOBACCO SMOKING – A PHARMACOKINETIC AND PHARMACODYNAMIC STUDY IN PATIENTS AFTER OPEN ABDOMINAL HYSTERECTOMY – A PILOT STUDY

DOROTA KOŁODZIEJ1, DANUTA SZKUTNIK-FIEDLER*, HANNA URJASZ2, TOMASZ GRABOWSKI1, RYSZARD BOSACKI4, EDMUND GRZEŚKOWIAK2, and EDYTA SZAŁEK2

1Pharmacy Department, Pleszewskie Centrum Medyczne, Poznańska 125a, 63-300 Pleszew, Poland
2Department of Clinical Pharmacy and Biopharmacy, Poznan University of Medical Sciences, Rokietnicka 3, 60-806 Poznań, Poland
3Polpharma Biologics SA, Preclinical Development, Trzy Lipy 3, 80-172 Gdańsk, Poland
4Gynecology and Obstetric Ward, Pleszewskie Centrum Medyczne, Poznańska 125a, 63-300 Pleszew, Poland

Abstract: Tapentadol (TAP) is the first representative of a new class of multimodal analgesics with a favorable safety profile, also applicable in postoperative pain. As a UDP-glucuronosyltransferase (UGT) substrate (in about 70%), TAP pharmacokinetics can potentially be influenced by UGT inducers or inhibitors. It is known that smoking can increase drug metabolism activity through UGT enzyme induction. Therefore, the study aimed to evaluate the pharmacokinetics of TAP after open abdominal hysterectomy (AH) in smoking compared to non-smoking tobacco patients. A single oral dose of TAP 100 mg was given to the patients on the first postoperative day after AH (n = 6, smoking and n = 8, non-smoking patients). Pain relief (Numerical Rating Scale, NRS), sedation, saturation, heart rate, and adverse effects were monitored. Blood samples were collected within 12 h after the drug administration. Smokers presented significantly lower Cmax and AUC0-t, and CL/F value was twice as high in this group. A moderately strong negative correlation between NRS scores and TAP concentration was revealed (R2 = -0.5231). Negative correlations between TAP concentration and life parameters: oxygen saturation and heart rate were observed. Significantly lower plasma concentrations and exposure to TAP in smoking patients after AH compared to non-smoking may indicate metabolic induction of UDP-glucuronosyltransferase by components of tobacco smoke. Since plasma concentration of TAP and NRS are negatively correlated, this may require consideration of TAP dose adjustments in smoking patients.

Keywords: abdominal hysterectomy, tapentadol, pharmacokinetics, pharmacodynamics, smoking patients

Open abdominal hysterectomy (AH) is a major surgical procedure that causes extensive tissue injury with significant pain (1). A rational strategy for controlling postoperative pain is multimodal analgesia (MMA), which reduces analgesic doses and has fewer side effects that may affect the patient’s recovery after surgery (2).

An example of multimodal analgesia in a single molecule is tapentadol (TAP), µ-opioid receptor agonist, and norepinephrine reuptake inhibitor (3). The dual mechanism of action of TAP contributes to its strong analgesic efficacy and reduced frequency of undesirable effects typical of classic opioids (3, 4). The agonist activity of TAP at the µ-opioid receptor is believed to be responsible for the alleviation of nociceptive pain (3), including acute postoperative (5-7), or cancer pain (8), and the noradrenergic mechanism of action to be effective in relieving various forms of neuropathic pain e.g., diabetic polyneuropathy (9) and back pain (10). TAP is also an analgesic with a low potential for drug-drug interactions (3). However, it is a UDP-glucuronosyltransferase (UGT) substrate in about 70%. Therefore, its pharmacokinetics can potentially be influenced by UGT inhibitors or inducers. For example, tobacco smoking can cause a significant induction of UGT activity.

Therefore, the study aimed at the pharmacokinetic evaluation of TAP after open abdominal hysterectomy (AH) in smoking compared to non-smoking patients.

* Corresponding author: e-mail: dszkutnik@ump.edu.pl
EXPERIMENTAL

Patients

The trial was carried out after obtaining the consent of the Bioethics Committee at the Poznan University of Medical Sciences (consent No. 167/16 of 03/03/2016). The study was performed following the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments and following the Regulation of the Polish Minister of Health of May 2, 2012, on the specification of detailed requirements of Good Clinical Practice (11). Written informed consent was obtained from all individual participants included in the study. The study group consisted of adult women who underwent AH (n = 6, smoking, and n = 8, non-smoking). The surgical procedure was similar in all patients. The main criteria for patient inclusion were: a complete or incomplete AH, pain on the numerical rating scale (NRS) from 4 to 10, and aged 18 years and over. Criteria for excluding patients from the study were: hypersensitivity to TAP, severe renal impairment, moderate and severe hepatic impairment, and a known history of addiction to opioids or other psychoactive substances.

The course of the study

Before the surgery, the patients have given midazolam 7.5 mg orally. All patients were treated with spinal anesthesia during the operation using 12.5-20 mg 0.5% bupivacaine and 0.05-0.1 mg iv fentanyl. On the day after surgery (day 0), patients received a continuous intravenous infusion of oxycodone in saline at a flow rate of 1.5-3 mg/h. On request, patients could also receive additional intravenous doses of analgesics: paracetamol, metamizole, and ketoprofen in maximum daily doses of 1 g, 5 g, and 200 mg, respectively. On the first postoperative day (day 1) in the morning, a 100 mg TAP was given to the patients (2 tablets of Palexia retard® 50 mg). After that, patients’ blood samples (3 mL) were collected at predetermined time points until 12.0 hours after TAP administration. Concentrations of TAP in the blood plasma were determined by a method published by Giorgi et al. (12).

Pharmacokinetic evaluation

The pharmacokinetics of TAP was determined by the use of the noncompartmental approach based on the statistical moment theory. The pharmacokinetic parameters: area under the plasma concentration-time curve from zero to the time of the last measurable concentration (AUC₀⁻), mean residence time from zero to the time of the last measurable concentration (MRT₀⁻), the apparent plasma drug clearance (CL/F), and apparent volume of distribution (Vd/F) were calculated using the Phoenix® WinNonlin version 8.0 software (Certara L.P., Princeton, New Jersey, USA). Maximum plasma concentration (Cₘₓ) and time to reach the Cₘₓ (tₘₓ) were obtained directly from the measured values.

Pharmacodynamic evaluation

After TAP administration at the same time points as blood sampling, the patient-declared pain levels on the 11-point NRS scale, blood saturation, heart rate, blood pressure, nausea (4-point scale),
and vomiting (number of episodes) were recorded. After taking the last blood sample in the evening, the patients received another 100 mg dose of TAP.

**Statistical analysis**

The statistical analyses of pharmacokinetic parameters were performed using the Statistica software (Statistica, Tulsa, OK, USA) version 13.3 (SAS Institute Inc., Cary, NC 27513, USA). Normality was estimated with the Shapiro–Wilk test. The differences between the normally distributed variables (AUC\(_{0-t}\), C\(_{\text{max}}\), MRT\(_{0-t}\), CL/F, Vd/F) were determined with the Student’s t-test. For the t\(_{\text{max}}\), the Mann–Whitney U test was applied. A p-value < 0.05 was considered significant.

**RESULTS**

Demographic patient characteristics (n = 14) are presented in Table 1.

Plasma pharmacokinetic parameters for TAP are presented in Table 2. TAP plasma concentration (ng/mL)-time profiles in smoking and non-smoking tobacco patients after single oral administration of TAP at a dose of 100 mg are shown in Figure 1.

Linear regression plots of declared pain (NRS scale), blood saturation (%) and heart rate (bpm) over time versus the TAP plasma concentrations (ng/mL) in patients (n = 14) after single oral administration of TAP at a dose of 100 mg are demonstrated in Figure 2, Figure 3, and Figure 4, respectively.

**DISCUSSION AND CONCLUSION**

TAP has not been considered susceptible to many interactions due to inconsiderable (15%) CYP450 metabolism and low (20%) protein binding. However, as a UDP-glucuronosyltransferase (UGT) substrate (70%), TAP pharmacokinetics can potentially be influenced by changes in UGT activity (3). Smoking has the potential for UGT induction (13); however previously published studies showed variable and, in some cases, inconsistent effects of

| Time [h] | Concentration [ng/mL] |
|---------|-----------------------|
| 0.5     | 0.5                   |
| 1.0     | 1.0                   |
| 2.0     | 2.0                   |
| 3.0     | 3.0                   |
| 4.0     | 4.0                   |
| 5.0     | 5.0                   |
| 6.0     | 6.0                   |
| 7.0     | 7.0                   |
| 8.0     | 8.0                   |
| 10.0    | 10.0                  |

Figure 1. TAP plasma concentration (ng/mL)-time profiles in smoking and non-smoking tobacco patients after single oral administration of TAP at a dose of 100 mg.

S – smoking patients (n = 6); NS – non-smoking patients (n = 8).

Figure 2. Linear regression plots of declared pain (NRS scale) over time versus the TAP plasma concentrations (ng/mL) in patients (n = 14) after single oral administration of TAP at a dose of 100 mg.

Figure 3. Linear regression plots of blood saturation (%) over time versus the TAP plasma concentrations (ng/mL) in patients (n = 14) after single oral administration of TAP at a dose of 100 mg.

Figure 4. Linear regression plots of heart rate (bpm) over time versus the TAP plasma concentrations (ng/mL) in patients (n = 14) after single oral administration of TAP at a dose of 100 mg.
DOROTA KOŁODZIEJ et al.

Tobacco smoking on drug glucuronidation, which may be dependent on UGT isoform and smoking intensity (13, 14).

In our study, TAP plasma concentrations in patients after AH were lower at every single time point in smokers than in nonsmokers (Figure 1). Such a relationship was observed regardless of the number of cigarettes smoked per day (lower than 10, between 10 and 20, and higher than 20). It was also noted that the analgesic effect of TAP increases with its plasma level. Ratio $R^2 = -0.5231$ indicates a moderately strong negative correlation between NRS scores and TAP concentration (Figure 2).

Pharmacokinetic parameters of TAP obtained in our study were similar to the results of Göhler et al. (15) and Huntjens et al. (16). We observed, however, that smokers presented significantly lower $C_{\text{max}}$ and $\text{AUC}_{\text{0-t}}$ values. Moreover, the CL/F value was twice as high in this group ($p = 0.0178$) (Table 2). Such results may indicate metabolic induction of UDP-glucuronosyltransferase by ingredients of tobacco smoke (13).

Patients in our study had various comorbidities or types of surgery (Table 1), although both smoking and non-smoking groups were similar. Also, we found no differences between the smoking and non-smoking group for BMI or age.

Also analyzed other medications taken chronically by the patients (levothyroxine, amlodipine, spironolactone, metoprolol, propranolol, torasemide, mesalazine, calcium, vitamin D, ursodeoxycholic acid, cetirizine) for possible interactions with TAP. None of these drugs exhibit potent UGT inhibition or induction properties. Due to suspected perioperative infection, only one patient from the smoking group received a single oral dose of metronidazole (one hour after TAP administration). Metronidazole is the known inhibitor of the UGT2B7 enzymes, responsible for the metabolism of TAP. Although this was a single administration, the enzyme activity should not be significantly affected.

Negative correlations between TAP concentration and life parameters: blood saturation ($R^2 = -0.5999$) (Figure 3) and heart rate ($R^2 = -0.2341$) (Figure 4) were observed. However, it is necessary to mention that all saturation values were high (> 90%) and didn’t pose a threat to patients’ health status. No correlation between pain level (NRS scale) and heart rate or saturation was found.

Limitations of the study

Wide PK parameters fluctuation was observed (Table 2). Described discrepancies are unavoidable in clinical research that is not performed in healthy volunteers. Obtained results, however harder to interpret than in a homogenous population, might be even more valuable in clinical practice.

| PK parameters | Smoking patients (n = 6) | Non-smoking patients (n = 8) | $p$-value* |
|---------------|--------------------------|----------------------------|------------|
| $C_{\text{max}}$ [ng/mL] | 41.87 ± 20.74; (49.54) | 68.84 ± 19.24; (27.96) | 0.0157 |
| $t_{\text{max}}$ [h] | 4.5 [2.0;6.0]; (31.53) | 3.5 [2.0;10.0]; (58.51) | ns. |
| $\text{AUC}_{\text{0-t}}$ [h × ng/mL] | 270.6 ± 139.8; (51.67) | 450.2 ± 170.5; (37.87) | 0.0259 |
| $\text{MRT}_{\text{a,t}}$ [h] | 5.73 ± 0.69; (12.01) | 5.43 ± 1.34; (24.59) | ns. |
| $V_d/F$ [L] | 2521.5 ± 1310.2; (51.96) | 1171.6 ± 537.8; (45.90) | 0.0266 |
| $\text{CL/F}$ [L/h] | 429.8 ± 185.5; (43.15) | 211.9 ± 116.1; (54.82) | 0.0178 |

Arithmetic means ± standard deviations (SD) and for $t_{\text{max}}$ median with minimum and maximum values (in square brackets) are shown with coefficients of variation (CV) (%) in brackets. $\text{AUC}_{\text{0-t}}, C_{\text{max}}, \text{MRT}_{\text{a,t}}, \text{CL/F}, V_d/F$ were determined with the Student’s t-test. For $t_{\text{max}}$ the Mann–Whitney U test was applied. A p-value < 0.05 was considered significant; ns. – not significant;

*Smoking patients vs. Non-smoking patients; $C_{\text{max}}$ – maximum observed plasma concentration; $t_{\text{max}}$ – time to the reach of $C_{\text{max}}$; $\text{AUC}_{\text{0-t}}$ – area under the plasma concentration-time curve from zero to the time of last measurable concentration; $\text{MRT}_{\text{a,t}}$ – mean residence time from zero to the time of the last measurable concentration; $V_d/F$ – apparent volume of distribution; $\text{CL/F}$ – apparent plasma drug clearance.

Table 2. Pharmacokinetic parameters of TAP in women after hysterectomy (n = 14) taking into account smoking tobacco patients.
CONCLUSION

Changes in the pharmacokinetics of TAP in smoking patients may indicate metabolic induction of UDP-glucuronyltransferase by ingredients of tobacco smoke. Since plasma concentration of TAP and NRS are negatively correlated, this may require consideration of TAP dose adjustments in smoking patients. When TAP is used in the treatment of postoperative pain, it should be taken into account whether the patient is a tobacco smoker.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Raghvendra K.P., Thapa D., Mitra S., Ahuja V., Gombar S., Huria A.: J. Midlife Health 7, 65 (2016).
2. Helander E.M., Menard B.L., Harmon C.M., Homra B.K., Allain A.V., et al.: Curr. Pain Headache Rep. 21, 3 (2017).
3. Faria J., Barbosa J., Moreira R., Queirós O., Carvalho F., Dinis-Oliveira R.J.: Eur. J. Pain 22, 827 (2018).
4. Channell J.S., Schug S.: Pain Manag. 8, 327 (2018).
5. Comelon M., Raeder J., Drægni T., Lieng M., Lenz H.: Eur. J. Anaesthesiol. 38, 995 (2021).
6. Ffrench-O’Carroll R., Steinhaeuser H., Duff S., Close J., McNamara J., et al.: Curr. Med. Res. Opin. 35, 975 (2019).
7. Hyland S.I., Brockhaus K.K., Vincent W.R., Spence N.Z., Lucki M.M., et al.: Healthcare (Basel) 9, 62 pages (2021).
8. Homma M., Kokubun H., Okuwaki K., Katada C., Hayashi N., et al.: Biol. Pharm. Bull. 43, 1000 (2020).
9. Alam U., Sloan G., Tesfaye S.: Drugs 80, 363 (2020).
10. Kern K.U., Sohns M., Heckes B., Elling C.: Pain Manag. 10, 85 (2020).
11. Regulation of the Minister of Health of 2 May 2012 on Good Clinical Practice, Poland. https://isap.sejm.gov.pl/isap.nsf/DocDetails.xsp?id=WDU20120000489 (accessed on 2016.02.15).
12. Giorgi M., Meizler A., Mills P.C.: J. Pharm. Biomed. Anal. 67, 148 (2012).
13. Court M.H.: Drug Metab. Rev. 42, 209 (2010).
14. Kuip E.J.M., Oldenmenge W.H., Thijs-Visser M.F., de Bruijin P., Oosten A.W., et al.: PLoS One 13, 7 pages (2018).
15. Göhler K., Brett M., Smit J.W., Rengelshausen J., Terlinden R.: Int. J. Clin. Pharmacol. Ther. 51, 338 (2013).
16. Huntjens D.R., Liefaard L.C., Nandy P., Drenth H.J., Vermeulen A.: Clin. Drug Investig. 36, 213 (2016).

© 2021 by Polish Pharmaceutical Society. This is an open-access article under the CC BY NC license (https://creativecommons.org/licenses/by-nc/4.0/).