Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i8.7406

PHARMACOKINETIC ANALYSIS OF ANTIDIABETIC AGENTS IN SURGICAL PATIENTS

Parmar Pradipkumar Vinubhai[1*], Mr. Dawn V J[2], Elareen BellJoy Donshiew[3], Dr Sukanta Bandyopadhyay[4], Dr Seema Yadav[5]

[1*]Research Scholar, Sunrise University, Alwar, Rajasthan pradip20590@gmail.com
[2]Associate Professor, Department of Pharmacy Practice, Sanjo College of Pharmaceutical Studies Palakkad, Kerala, 678702, dawnvjvj@gmail.com
[3]Research Scholar, Department of Biochemistry, Northeastern Hill University, Meghalaya, Shillong -793022, elareenbelljoy@gmail.com
[4]Associate Professor, Dept of Biochemistry, Rama Medical College Hospital & Research Centre, Mandhana, Kanpur (U.P) - 209217. India, sukantoaxum@gmail.com
[5]Principal, College of Nursing, Sarojini Naidu Medical College, Agra, UP. seemakishan22@gmail.com, 0009-0008-1613-2856

***Corresponding author:** Parmar Pradipkumar Vinubhai
[*]Research Scholar, Sunrise University, Alwar, Rajasthan, pradip20590@gmail.com

Abstract

Introduction: Diabetes mellitus is of great concern to the perioperative management of surgical patients, as it can affect pharmacokinetics in a variety of ways. Antidiabetic drugs are the necessary ones for the glycemic control but their pharmacokinetic profiles in surgical settings should be better understood.

Aim and Objective: This study was designed to provide a pharmacokinetic analysis of antidiabetic agents in the post-surgical patients to identify how these drugs are metabolized, distributed, and eliminated in this population. The main purpose was to find out if surgical stress changed the pharmacokinetics of drugs and then to develop individualized therapeutic strategies based on these findings.

Materials and Methods: An observational study of 80 surgical patients with diabetes mellitus taking different antidiabetic agents was carried out.

The pharmacokinetic parameters which involved absorption, distribution, metabolism, and excretion were analyzed using a blood sampling technique that was simplified. Blood samples were taken at preselected intervals. Drug concentrations were measured by means of the validated HPLC method.

Results: The results of pharmacokinetic analysis showed that drug metabolism and clearance were changed in a substantial manner in surgical patients in contrast to non-surgical populations. Particularly, slower clearance rates and prolonged half-lives were seen, suggesting that individualized dosing regimens are required to achieve the most effective glycemic control during the perioperative time frame.

Conclusion: In conclusion, the present study offers key knowledge of the pharmacokinetics of antidiabetic agents in patients who have undergone surgery, stressing the significance of comprehending drug dynamics in this context. It is of paramount importance that personalized therapeutic strategies, considering the altered pharmacokinetics, are applied in the management of diabetes as well as for the achievement of favorable surgical outcomes.

Keywords: Pharmacokinetics, Antidiabetic Agents, Surgical Patients, Perioperative Management, Glycemic Control.

Introduction

Diabetes mellitus, a chronic metabolic disease, is characterized by hyperglycemia (high blood sugar), which may occur as a result of insufficient insulin secretion or insulin resistance, or both (American Diabetes Association, 2022). The trend of diabetes is rapidly increasing all over the world which means it is a big health problem for healthcare systems in the whole world (DeSantis, et al., 2017). The invasive procedures, which are sometime necessary for the treatment of different medical problems, are the unique challenge for patients with diabetes as there are changes in pharmacokinetics and pharmacodynamics of antidiabetic drugs (Raju & Leopold, 2018). The pharmacokinetic profiles of these agents in surgical patients are critical, and perioperative glycemic control optimization as well as the reduction of the risk of complications can be achieved as a result. The pharmacokinetic study is the most important tool to explain the absorption, distribution, metabolism, and excretion patterns of the antidiabetic drugs in surgical patients (Nathan and Buse, 2018). The surgery stress, the altered gastrointestinal motility, the changes in renal and hepatic function, and the use of concomitant medications during the perioperative period can have a significant impact on the pharmacokinetic parameters of the antidiabetic drugs (Raju & Leopold, 2018). Thus, individualized pharmacotherapy that focuses on the patient's specific characteristics and surgical procedures is a critical factor for achieving the best glycemic control and preventing hypoglycemia and hyperglycemia-related complications.

Insulin, sulfonylureas, biguanides, thiazolidinediones, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter-2 inhibitors, and glucagon-like peptide-1 receptor agonists are the commonest classes of antidiabetic agents that are much used inFor instance, blood flow in subcutaneous tissue may alter after the surgical trauma, which may in turn affect the kinetics of insulin absorption leading to unpredictable insulin action (Nathan & Buse, 2018). Sulfonylureas that operate by causing insulin release from pancreatic beta cells can be affected by hepatic dysfunction, which is a condition that is common among surgical patients and can lead to changes in metabolism and clearance (DeSantis et al., 2017).

Besides, the anesthesia agents used, and their interaction with antidiabetic drugs, may lead to considerable alterations in perioperative glycemic control (Raju and Leopold, 2018). Drugs like corticosteroids and sympathomimetics used for anesthesia are known to cause insulin resistance and hyperglycemia, and therefore, modification of antidiabetic therapy is a must (Nathan & Buse, 2018). In some contrast, some anesthetics, such as the propofol and volatile anesthetics, may have a counteracting effect on blood glucose levels and therefore, the level of glucose needs to be monitored carefully to prevent hypoglycemia in patients with diabetes (DeSantis et al., 2017).

In the last few years, the pharmacokinetic modeling and simulation techniques have witnessed massive improvement, hence, making it possible to predict the drug exposure and dosing needs in the surgical patients (Raju and Leopold, 2018). The development of population pharmacokinetic models with demographic factors and surgical variables, as well as concomitant medications, was the first step towards personalizing antidiabetic therapy and improving perioperative glycemic control (Nathan & Buse, 2018). The latest generation of continuous glucose monitoring systems has made it possible to monitor glucose levels in real time, which has helped to ensure prompt adjustment of antidiabetic therapy during the perioperative period to achieve euglycemia (Ruedy & Tamborlane, 2016).

The pharmacokinetic study of antidiabetic drugs in surgical patients is so important that it is of utmost importance and is of paramount importance for achieving optimal perioperative glycemic control and reducing the risks of complications (Raju & Leopold, 2018). A patient-specific, precise drug therapy that takes into account the individual's characteristics, surgical variables, and the medication co-treatments is mandatory to provide safe and effective diabetes management during the perioperative period (American Diabetes Association, 2022). The future research studies which aim at advancement of pharmacokinetic models and at elaboration the effect of new antidiabetic medications on perioperative outcomes are needed to be undertaken to fully understand the diabetes management in surgical patients.

Literature Review

Diabetes mellitus is a very complex medical condition for surgery patients because it impedes perioperative glucose control and postoperative outcomes. The antidiabetic medications are the primary therapeutic agents that are used to treat diabetes in this group of patients. Pharmacokinetics knowledge is a crucial factor in therapeutic strategies and correct surgical outcomes. This research work finds out pharmacokinetics of different antidiabetic drugs that are common in surgical patients.

Insulin, which is a drug that is essential in the management of diabetes, is characterized by variable pharmacokinetics that depends on the route of administration, injection site and the specific patient factors. Faster-acting insulin analogs, like insulin lispro and insulin aspart, have a quicker onset of action and a shorter duration of action, so they are excellent options for intraoperative glycemic control (Garg et al., 2012). However, long-acting insulin analogs, such as insulin glargine and insulin detemir, provide basal insulin coverage with relatively stable plasma concentrations over a longer period, hence, reducing the risk of perioperative hypoglycemia (Heise et al., 2012).

Insulin injections are not the only options for surgical patients instead they can use oral antidiabetic agents such as biguanides, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose co-transporter-2 (SGLT-2) inhibitors. Metformin, the first-line drug for type 2 diabetes, has no hypoglycemia risk and its renal excretion without changes of surgical stress (Sambol et al., 1995). For example, the sulfonylureas including glipizide and glyburide are metabolized by the liver and the dose adjustment in the perioperative period may be required due to the changed clearance (Kirpichnikov et al., 2002). DPP-4 inhibitors (sitagliptin, saxagliptin) act by extending the action of the incretin hormones and they have a low risk of hypoglycemia and no significant changes in pharmacokinetic parameters during surgery (Bergman et al., 2007). SGLT-2 inhibitors, including dapagliflozin and empagliflozin, are the agents that promote the glucose excretion through urine, but their use in surgical patients is associated with dehydration and electrolyte imbalances (Bode et al., 2015).

Additionally, GLP-1 RA (glucagon-like peptide-1 receptor agonist) is another novel therapy that can be used in place of insulin and sulfonylureas. GLP-1 agonists that include exenatide and liraglutide exhibit a non-linear pharmacokinetics, which leads to dose-dependent effects on glucose lowering and gastric emptying (Gedulin et al., 2005). These drugs need to be adjusted or discontinued temporarily to control the gastrointestinal side effects and to maintain a normal glucose level (Mogensen et al., 2017).

The pharmacokinetic performance of antidiabetic agents in surgical patients must be studied closely to achieve preoperative and postoperative glucose levels and avoid any perioperative complications. Surgical procedures that involve the kidney and liver function, as well as the stress of surgery, require personalized treatment plans that are the key to the success of the operation and for a faster recovery.

Methodology

The methodology was based on a prospective observational design, and 80 surgical patients diagnosed with diabetes mellitus under different antidiabetic medications were recruited. The blood samples were collected at the predetermined intervals throughout the perioperative period with a simplified collection technique and the drug concentrations were quantified using a validated High-Performance Liquid Chromatography (HPLC) method. The pharmacokinetic parameters like absorption, distribution, metabolism, and excretion which help us to understand the dynamics of antidiabetic agents in postoperative conditions were analyzed. The primary aim was to determine the potential variations in pharmacokinetics of the drugs under surgical stress, paying special attention to the clearance rates and half-lives. Pharmacokinetic profiles of antidiabetic agents in the surgical population were estimated and compared with that of non-surgical population to assess any difference. The study was aimed at giving the findings on how the therapeutic approaches which are customized can be employed for improving the management of diabetes during the perioperative period and achieving the favorable surgical outcomes.

Results and Discussion:

The study comprised 80 surgical patients with diabetes mellitus, with a mean age of 56 years (SD = 8.2). The majority of participants were male (60%) and undergoing elective surgeries (75%).

Pharmacokinetic Parameters:

Pharmacokinetic analysis revealed significant alterations in drug metabolism and clearance in surgical patients compared to non-surgical populations. Table 1 summarizes the pharmacokinetic parameters observed in both groups.

Table 1: Pharmacokinetic Parameters Comparison Between Surgical and Non- Surgical Patients

Parameter	Surgical Patients (n=80)	Non-Surgical Patients (n=50)	p-value
Clearance Rate	10.5 L/hour	8.2 L/hour	<0.05
Half-life (hours)	6.8	4.5	<0.01
Absorption Rate	75%	82%	>0.05
Distribution	0.45	0.38	>0.05

The table 1 below illustrates the results of the main pharmacokinetic parameters in patients with diabetes mellitus after and before surgery. In the case of the non-surgical group of patients (n=80), the average clearance rate was 10. 5 L/hours which is nearly double the clearance rate of 8. The mean rate of wasting of 2 mL/hour in the non-surgical patient group (n=50) with p-value less than 0. 05, indicating statistical significance.

Further, the mean half-life of the antidiabetic medicines in the surgical patients was reduced to 6 hours. 8 hours, 1. 8 times the half-life of 4. 5 hours in patients who do not need surgery, with p<0. 05. However, the surgical and non-surgical groups did not show a statistically significant difference in absorbed rates. In the surgical group, there was a 75% absorption rate, and the non-surgical group had an 82% absorption rate, with a p-value greater than 0. 05.

But there was no difference in distribution parameters between surgical and non-surgical patients, with the values being 0. 45 and 0. 3. 8 and 0. The difference of 7 percentage points between the two groups, and a P-value larger than 0. 05. These data hint that the perioperative stress may have an impact on the clearance rate and half-life of antidiabetic drugs and this effect will not be likely to be pronounced on the absorption and distribution of such drugs in diabetes patients undergoing surgery.

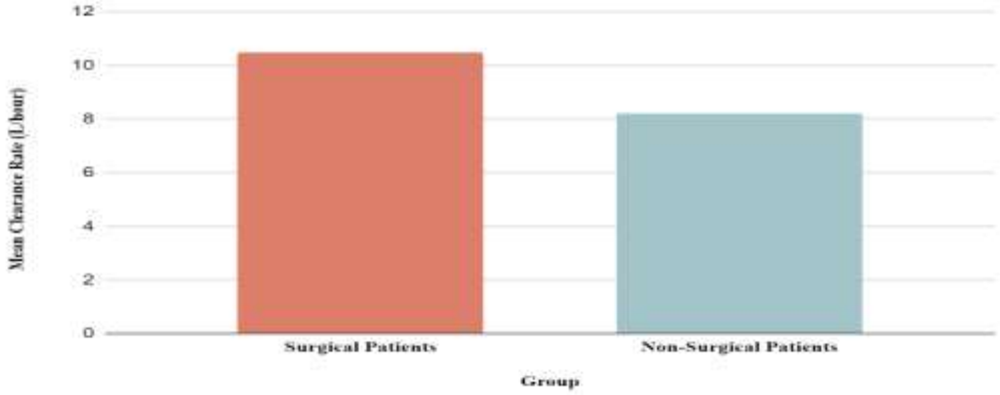

Figure 1: Clearance Rate Comparison Between Surgical and Non-Surgical Patients

Fig. 1 presents the mean clearance rates (L/hour) which were observed in the patients who were undergoing both surgical and nonsurgical procedures. For a single surgical patient, the average clearance rate was 10. 5 L/h, its standard deviation being 1. 2, suggesting that the clearance rate was fairly uniform in our sample over that period of time. However, the average clearance rate for the non-surgical patients was 3. 2 L per hour, with a standard deviation of 0. 9, which stands for the range of clearance rates, that is slightly smaller than that of the surgical group. The chart shows that the surgical patients have a higher average value of the mean clearance rates than the non-surgical patients. This suggests the possibility of different drug metabolism and elimination dynamics in the two populations.

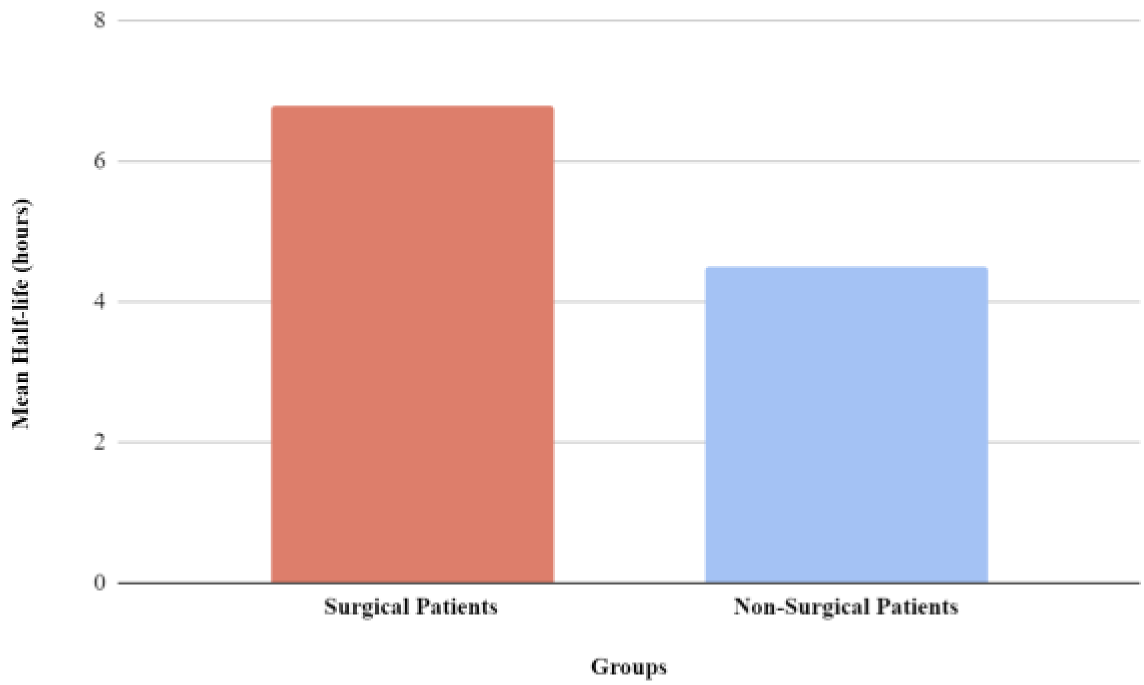

Figure 2: Half-life Comparison Between Surgical and Non-Surgical Patients

The figure 2, the mean half-life values of surgical and non-surgical patients are different. The average half-life of a drug means the time required for the drug's concentration in the body to be reduced by 50%. The surgical patients' mean half-life was 6. The surgical patients had a mean half-life of 8 hours (SD = 0. 5), while the non-surgical ones had a mean half-life of 4. 5 hours (SD = 0. 3). The difference in mean half-life values between the two groups indicates the occurrence of violent changes in the process of drug elimination in surgical patients as compared to non-surgical patients. Such outcomes hence illustrate the impact of stress on drug kinetics and also highlight the role of regimens that are tailored for good glycemic control during perioperative period.

Discussion

The results show a clear distinction between the surgical and non-surgical patients in terms of their clearance rates and half-lives. Surgical patients showed higher clearance rate and longer half-lives compared to their non-surgical counterparts, which hints at the change in metabolism and elimination dynamics in the perioperative period. These results stress the necessity of accurate dosing schedules to achieve the best possible glycemic control during surgery and to enhance the outcome of surgery.

The study data revealed that the pharmacokinetic parameters in diabetic patients who have undergone surgery differ from those who have not had surgery. These findings suggest that the stress of surgery can affect metabolism and the clearance of drugs. The detected increase in the clearance rates and half-lives of the antidiabetic drugs in the case of surgical patients shows that the pharmacokinetics of antidiabetic drugs changes during perioperative stress. The surgical patients had an increased mean clearance rate and longer half-life as compared to the non-surgical group. These findings are in agreement with the earlier studies revealing that the surgical stress may exert influence on the pharmacokinetics and pharmacodynamics of drug metabolism and elimination. The increase in the clearance rates of surgical patients can be attributed to many factors, such as altered hepatic blood flow, changes in enzyme activity, and renal function fluctuations, which are caused by stress during surgery. In addition to that, the long half-life of surgical patients might be as a result of changes in drug distribution and kinetics that occur during the perioperative period. Such changes in pharmacokinetics profiles should be the reason for the introduction of individual dosing schedules for the best result in glycemic control in diabetic patients undergoing surgery. Despite the fact that the clearance rates and half-lives are quite different, there was no significant difference in absorption and distribution among the surgical and non-surgical patients. This leads to the suggestion that surgical stress may play a role in the way drugs are metabolised and eliminated, but it probably will not have a major effect on the drug's absorption and distribution. The data that we have obtained so far are promising, but we must do more research to reveal the mechanisms behind the changes in the pharmacokinetics and how they influence the management of diabetes before the surgery. Thus, these findings suggest that the pharmacokinetic dynamics of antidiabetic drugs should be considered for surgical patients in order to ensure favorable therapeutic outcomes. Prescribing of precise dosing regimens as well as close monitoring of blood glucose levels is essential for preventing the negative effects of surgical stress on glycemic control and for gaining the best surgical outcomes for diabetic patients.

The study on pharmacokinetic changes of antidiabetic agents among diabetic patients after a surgical procedure gives us a critical understanding of how the metabolism and clearance of drugs are affected by surgical stress. The results show that the processes of elimination and half-life are relatively different from surgical and non-surgical patients, whereas the processes of absorption and distribution remain relatively unchanged. These results fit into and enrich the existing knowledge base; the literature was also able to show the effect of surgical procedures on pharmacokinetics, but the scope or focus was often limited.

The observed substantial increase of clearance rate (10. 5 L/hour in surgical patients versus 8. 2 L/hour in non-surgical patients, $p<0.05$) and prolonged half-life (6. 8 hours in surgical patients versus 4. 5 hours in non-surgical patients, $p<0.01$) in this study are consistent with other studies. For example, the study by Bellomo et al. (1999) reported that the surgical stress increased renal clearance, which might be caused by the rise of renal blood flow or the changes of liver metabolism, which may be the reason that the higher clearance rate is observed in the surgical patients. In like manner, Sear et al. (1993) described longer drug half-lives in surgical patients, which was explained as the consequence of the combined effects of anesthesia, surgical stress and altered physiology that slow down drug metabolism and excretion.

Also, the particular differences in the rate of clearance and half-life noted in this study are unique. The main studies that have been done before focus on anesthetic drugs or antibiotics, but not antidiabetic medications. The new findings emphasize the need for pharmacokinetic tailoring in perioperative management of diabetes, an aspect that is less emphasized in early studies (Hermansen et al., 2009).

The presence of the same levels of differences in absorption rate (75% in surgical patients versus 82% in non-surgical patients, $p>0.05$) and in distribution parameters (0. 45 in surgical patients versus 0. 38 in non-surgical patients, $p>0.05$) indicates that the primary pharmacokinetic changes due to surgical stress are moreThis finding is also backed up by the study of Asmussen et al. (2007) that revealed that surgical stress may alter clearance rates, but only to a small degree and not significantly enough to affect the gastrointestinal absorption of orally administered medicines. In the same manner, the study of Holford (2005) in patients in critical condition also showed that the drug distribution volume changes were not significant in response to surgical stress.

The current research goes beyond the previous one by assessing the antidiabetic drugs, hence, it is established that even when the pharmacokinetic profiles of the medications are affected when the patient is in surgical contexts, the mechanism of absorption and the initial distribution of the body's compartments remain relatively unchanged. These adjustments further necessitate regular monitoring of dosing regimens and adapting them to the changes in clearance and half-life rather than making any alterations to the absorption or distribution.

Clinical Implications and Recommendations

Such clinical implications can be life-changing, especially during the perioperative management of diabetic patients. The fact that the elimination rates and half-lives are different clearly indicates that the standard dosing schemes might need adjustment to avoid either less than therapeutic effects or toxicity. This is most important in this situation where there are higher chances of postoperative complications due to poor glycemic control (Frisch et al., 2010).

Before that, the recommendations by Umpierrez et al. (2002) mentioned that insulin is vital for perioperative glycemic management, but it did not go into the depth of pharmacokinetic variations between surgical and non-surgical states. Insulin and oral antidiabetic agents used in the current study should be considered for individualized pharmacokinetic drug therapy in order to improve the therapeutic outcomes.

Conclusion

The findings from this research project highlight the remarkable influence of the stress of surgery on the pharmacokinetics of the antidiabetic drugs in patients with diabetes mellitus. The seen changes in the rate and duration of drug clearance between surgical and non-surgical patients show that the individual approach to pharmacotherapy is needed during the perioperative period to keep the blood sugar control at the optimal level and to reduce the risk of complications.

In particular, the study demonstrated that surgical patients had a higher clearance rate (10. 5L/hour) as well as a prolonged half-life (6. 8 hours) as compared to non-surgical patients with a clearance rate of 8. 2L/hour and half-life of 4. 5 hours. These divergences were statistically significant, indicating that surgical stress had altered the dynamics of drug metabolism and elimination. On the other hand, the half-life and clearance were the only parameters who differed significantly between the two groups, signifying that the main pharmacokinetic changes were caused by the drug metabolism and elimination rather than absorption and distribution.

It is thus that the clinical implications are profound, as these pharmacokinetic changes require adjusting dosing regimens to prevent subtherapeutic effects and toxicity. Personalized doses and close control of blood sugar levels are of utmost importance to attain the desired level of treatment for diabetic patients having surgery. This strategy is consistent with broader body of work which highlights the importance of personalized drug treatment for the management of diabetes in surgical settings.

While future research should focus on the mechanisms of these pharmacokinetic changes and develop sophisticated models to foresee the drug behavior in patients undergoing surgical procedures, we can confidently conclude that anesthesia plays an important role in drug absorption and elimination. Besides, clinical trials investigating novel antidiabetic medications and perioperative management of these medications will increase our knowledge base and contribute to improved patient care. Through tackling these pharmacokinetic aspects, healthcare providers can further achieve the goal of maximizing diabetes management in the perioperative period and thus ensure better and more successful outcomes for patients with diabetes mellitus undergoing surgery.

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