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Original Article

ANTICONVULSANT ACTIVITY OF BUCCAL FILM MUCOADHESIVE SODIUM VALPROIC IN PENTILENETETRAZOLE INDUCES-SEIZURE MODEL

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Abstract

Epilepsy is a brain disorder characterized by a tendency to produce persistent epileptic seizures with neurobiological, cognitive, psychological and social consequences. the mucosal lining of the buccal region has highly vascularized, a decreased enzymatic activity, less sensitivity, ease of administration and expulsion of dosage form in the case of undesirable effects, avoiding acid hydrolysis of the stomach and bypassing hepatic first pass-effect and buccal administration exhibits better patient adherence in contrast to other non-oral drug-delivery routes. Objective of this research to determine the antiepileptic activity and drug release of sodium valproate in the form of buccal mucoadhesive film. Mucoadhesive Sodium Valproate Anti-epileptic activity test with pentylenetetrazole induction and sodium valproate drug release test were performed on wistar strain rats. The research to be carried out is an experimental study with a post randomized controlled group design with test all animals as objects were induced by pentylenetetrazol The test animals were divided into two research groups, namely the anti-epileptic activity test that will be carried out, namely the anti-epileptic activity test and the sodium valproate drug release test to compare the drug release in the form of sodium valproate solution, sodium valproate oral extended release (ER) and buccal preparations. The results of testing for anti-epileptic activity and pharmacokinetics showed that the buccal film mucoadhesive preparation had anti-epileptic activity with a longer duration of onset, shorter seizure duration, and lower seizure frequency when compared to the negative control group and the extended release group of sodium valproate tablets, pharmacokinetic profile. sodium valproate with absorption parameters Ka 0.003329345 Hr-1, Tmax 720.32 Hr-1, Cmax 248.87 mg/L, Vd 3.03 L, T1/2 el 411.05 minutes and Kel 0.016048 L /minutes.

Keywords : Anti Epilepsy, Pentilentetrazole, Sodium valproate

INTRODUCTION

Sodium valproate[1] has a broad spectrum of anticonvulsant activity, but is structurally unrelated to conventional antiepileptic drugs. Its proposed mode of action is mediated through effects on the function of brain γ-aminobutyric acid (GABA). However, the elevations in brain and cerebellar GABA, and the concomitant reductions in levels of cyclic guanosine

monophosphate, occur in animals at dose levels which are unlikely to be achieved during the treatment of epileptic patients. Sodium valproate is an antiepileptic drug that is effective in inhibiting absence seizures, partial seizures and tonic-clonic seizures. The mechanism of action of sodium valproate in the treatment of epilepsy is by increasing the inactivation of Na+ channels, thereby decreasing the ability of nerves to conduct electrical charges. (Perucca, 2002)

Despite all these efforts, successful therapy of sodium valproate in treating epilepsy diseases remains elusive. In this context, we hypothesize that the buccal drug delivery route could be a promising approach for the delivery of sodium valproate. Drug delivery through the buccal route offers rapid and direct delivery into the systemic circulation, bypassing any degradation in the gastrointestinal tract and the first-pass metabolism in the liver. This increases the bioavailability of the drug as well as provides a steady state plasma drug level, which in turn increases the therapeutic efficiency.(Virmani *et al*., 2015)

The induction model using pentilentetrazole (PTZ) is not well known. PTZ is a selective antagonist of receptor of GABAA chloride ionophore complex and Pentylenetetrazole (PTZ)-induced seizures is one of the gold standard mouse models for rapid evaluation of novel anticonvulsants.(Ergul Erkec, 2015) .

Moreover, this drug delivery route is also preferred for targeted, controlled and sustained release of drug molecules. Considering the significance of the buccal route, the objective of this study was to assess the feasibility of delivering sodium valproate through the oral mucosa by preparing buccoadhesive films. Formulation development was aimed on developing buccoadhesive films, which could provide quicker onset of action, prolonged drug release and improved bioavailability. The prepared films were characterized and the in vitro and in vivo evaluation of dosage form was performed. Furthermore, the effect of different polymers on the mucoadhesion time of buccal films and factors influencing drug release from the film were studied.

METODOLOGY

MATERIAL

The tools used in this study were Double Beam UV/Vis Spectrophotometer (Simadzu 1280), Analytical Scale (OHAUS Pioneer) with a sensitivity of 0.0001 g, Micro Pipette (SOCOREX) 50 – 1000 L, centrifuge (Effendorf Minispin), animal cages test, hematocrit pipe, glass tools such as measuring flasks, beakers, measuring cups and test tubes as well as other laboratory support equipment.

The material used for this experiment is Sodium valproate obtained from PT. Otto Pharmaceutical Lab which has been formulated into Buccal mucoadhesive dosage forms, Depacote® Extended Release (AbbVie Ltd, Imported and packed by PT. Abbott Indonesia), Chitosan from Sigma Aldrich, Carboxymethylcellulose-Na, Propylene glycol, Pharmacoat

604, Acetic acid, Animal Test Wistar white rats were obtained from the Pharmacy Study Program of the National College of Health Sciences.

Pentylenetetrazole from Sigma Aldrich, Na EDTA, Ketamine, Wistar strain White Rat Test Animals were obtained from the Pharmacy Studies Program of the National College of Health Sciences.

The research to be carried out is an experimental study with a Post Randomized Controlled Group Design with test animals as objects. The test animals were divided into two research groups, namely the anti-epileptic activity test that will be carried out, namely the anti-epileptic activity test and the sodium valproate drug release test to compare the drug release in the form of sodium valproate solution, sodium valproate oral extended release (ER) and buccal preparations. Mucoadhesive Sodium Valproate. Anti-epileptic activity test with pentylenetetrazole induction and sodium valproate drug release test were performed on wistar strain rats.

In this test, Pentylenetetrazole (PTZ) is used which is a chemical compound that can induce seizures by binding to the GABA-A receptor. This compound is widely used to induce seizures in test animals to test the activity of an anticonvulsant.

This study used 4 groups of test animals so that the results of calculations using the Federer formula obtained the results of n 6, so the number of samples for each group was 6 test animals, namely:

1) The group of white rats used as a negative control (SCMC suspension 0.5%).
2) A group of white rats given i.p. Sodium valproate at a dose of 100 mg/KgBB
3) The group of white rats treated with Optimum Formula of Buccal Buccal film sodium valproate dosage 250 mg
4) The group of white rats treated with 250 mg ER sodium valproate tablets

All test animals in the group were given treatment followed by 15 minutes and then induced by Pentylenetetrazole (PTZ) at a dose of 80 mg/KgBW which had been dissolved in 0.9% NaCl. Observations were made on the onset, duration, frequency, with a length of observation for 12 hours. Then compared between the dose groups with positive and negative control groups. Onset was counted from the injection of pentylenetetrazole until the time of the seizure. The duration was calculated from the start of the seizure to the end of the seizure. While the frequency is the number of seizures that occur. The seizures observed in this study were tonic-clonic seizures. Referring to Erkec and Arihan (2015), the Seizure score after 30 minutes of PTZ injection was defined Phase 0: No response, Phase 1 Ear and facial twitching, phase 2 myoclonic body jerks, phase 3 clonic forearm seizures, phase 4 generalized clonic

seizures, changes to one side position, phase 5 generalized clonic-tonic seizure (or death) within 30 minutes, phase 6 Death.

1. In Vivo Anti Epilepsy Activity Test

Anti-epileptic activity can be determined by observing the time of onset, duration, frequency, and number of deaths in test animals for each treatment group. The mean of onset, duration, number of seizures and number of deaths in the treatment group was compared with the control group. Observation of seizure conditions in test animals caused by pentilentetrazole induction included 5 phases, namely phase 1 of the ear and face twitching, phase 2 of myoclonic body jerks, phase 3 of clonic forearm seizures, phase 4 of generalized clonic seizures, changing to one side position, phase 3 of generalized clonic seizures. 5 generalized clonic-tonic seizures (or death) within 30 minutes, phase 6 Death.

The results of the study mean SD onset, duration, number of seizures and number of deaths in each group can be seen in Table 4.5. Based on Table 4.5 and the results of statistical analysis of the four parameters, the following results were obtained:

Tabel 1. The results of observations of PTZ .-induced generalized tonic-clonic seizures in test animals

Group	Mean ± SD			
	Seizure onset (second)	Seizure Duration (second)	Number of Seizure Frequency	Number of Deaths (%)
I	46,83 ± 8,76	1015,50 ± 523,39	6 ±1,11	3
II	1088,3 ± 100,02	223± 46,52	1 ± 0	0
III	404,33 ± 89,57	817,17 ± 88,02	3 ±0,69	0
IV	758,67 ± 90,15	591,17 ± 100,93	1 ±0,69	0

Group I : Negative Control (suspensi SCMC 0,5%).
Group II : Treatment with i.p sodium valproate dose 100 mg/KgBB
Group III : Treatment with sodium valproate tablets ER dosis 250 mg
Group IV : Treatment with muchoadhesive buccal film sodium valproate dose 250 mg

The results of this test prove that the activity of the antiepileptic drug sodium valproate works through the mechanism of increasing GABA, producing an anticonvulsant effect by increasing GABA-ergic neurotransmission that has been inhibited by PTZ. Between the treatment groups had differences in the outcome of seizure onset, seizure duration. The data in

Table 4.5 shows that in all treatment groups of test animals with $P < 0.05$, which means that the treatment group gave a significant difference with the negative control group, this effect was seen from the effect that it could prolong the onset of seizures. The results showed that the buccal film mucoadhesive preparation of sodium valproate showed a longer duration of onset, shorter duration of seizures, and lower seizure frequency when compared to the negative control group without treatment and the group receiving extended release sodium valproate tablets. Although it was still better when compared to the i.p administration group, sodium valproate solution was able to prolong the onset, shorten the duration, frequency of seizures and there were no deaths in PTZ-induced test animals.

2. Standard Curves

The purpose of making a standard curve is to obtain a standard curve equation that is used to calculate the concentration of sodium valproate samples. This standard curve equation was obtained by measuring each concentration series of sodium valproate standard solution at a wavelength of 361 nm and continued by making a regression line equation between concentration as the independent variable and absorption as the dependent variable. The results of the absorption measurement series of standard solution levels and standard curve regression equations are shown in Table 2 and Figure 1.

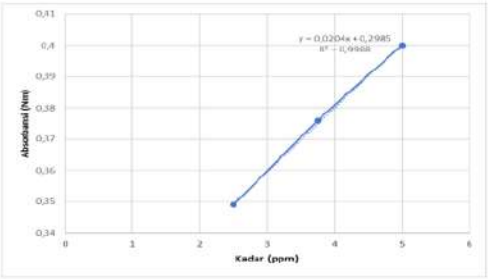

Figure 2. Standard Curve of Sodium valproate

From the curve of Figure 2 it can be seen that an increase in sodium valporate content will result in an increase in absorbance with a linear relationship. Results The equation of the line obtained is as follows: $y = 0.0204x + 0.2985$. a valid bioanalytical method, the linearity criteria were met by producing the coefficient of variation $r = 0.998$. Which is then used to determine the level of sodium valporate in plasma.

2. Determination of Recovery Value, random error and systematic error

After determining the standard curve equation, the recovery value, random error and systematic error are determined. The recovery value is a measure of the accuracy of the analysis. Random error is synonymous with measurement variability. The results of the study

in table 3 show that the resulting accuracy range is still within the limits of 80% to 120% and the coefficient of variation value is below 15. The analytical method is said to be a valid method if it has a recovery value in the range of 80-120%, random error is below 10% and systematic error below 10%.

Tabel 3. Recovery, random error and systematic error

Content (ppm)	Abs	Recovery, Accuracy	Mean	SD
2,5	0,351	102,94	99	3,20
2,5	0,347	95,098		
2,5	0,349	99,02		
3,75	0,373	97,386	94	2,22
3,75	0,369	92,157		
3,75	0,37	93,464		
5	0,4	99,51	96	4,62
5	0,39	89,706		
5	0,4	99,51		

2. Determination of sodium valproate in plasma

Based on the pharmacokinetic profile data, the absorption phase was indicated by the values of t max, C max and K abs. The dosage form and route of administration affect the difference in the maximum level of sodium valproate in the systemic circulation. Cmax i.p NP 187.31 mg/L, Cmax tablet ER NP 244.54 mg/L and buccal film mucoadhesive NP 248.87 While the time required for maximum drug concentration if sorted from shortest, namely i.p NP at 70.78 minutes , buccal film mucoadhesive NP 720.32 and tablet NP ER 1079.85.

Kabs which describes the rate of absorption, namely when the drug enters the systemic circulation from the absorption site. Ka abs was given i.p. NP 0.01723065, buccal film mucoadhesive was 0.003329345 and NP ER tablet was 0.002253996. The absorption rate of buccal film mucoadhesive preparations was slower than i.p administration but slightly higher than that of ER NP tablets. T max pemberian i.p NP 70,78, Mukoadhesif film bukal 720,32 dan pemberian tablet NP ER 1079,85.

The distribution phase can be seen from the value of the volume of distribution (Vd). The greater the value of the volume of distribution, the smaller the level of drug in the blood because in this phase the drug has spread to body tissues and is sorted from the largest Vd value, namely i.p. NP 19.03, tablet NP ER 6.88 and buccal film mucoadhesive NP 3.03. Volume of distribution is the volume of distribution that is pharmacologically used to determine the amount of drug distribution in plasma and will remain in the body after oral or

parenteral use. It defines the volume of drug required to be distributed and produces a preview of the drug concentration in the blood

The elimination phase is described by the clearance value (Cl), which is the volume of blood that is cleared of the drug present in the body. The Cl value obtained from the highest administration of i.p NP 0.21732 mL/minute, buccal mucoadhesive film 0.016048 mL/minute and administration of ER NP tablets 0.06739 mL/minute, stated that every 1 minute the amount of blood cleaned was 0.016048 mL.

AUC Total administration of i.p NP 29919,4853, buccal film mucoadhesive 239061,3453 and administration of ER NP tablets 195470,6046, where the higher the concentration at each time, the greater the AUC value for that time, and the longer t1/2 the drug the more the time required to reduce the drug concentration by half. The results of the study concluded that the development of sodium valproate preparations in the form of buccal mucoadhesive films could affect the pharmacokinetic profile of sodium valproate.

Tabel 4.4 Pharmacokinetic Data Parameters

Parameter	i.p administration	Tablet NP ER	NP Buccal Film Mukoadhesive
Ka (Hr-1)	0,01723065	0,002253996	0,003329345
T1/2 abs (/minute)	40,21	307,45	208,14
Tmax (hr-1)	70,78	1079,85	720,32
Cmax (mg/L)	187,31	244,54	248,87
AUC total	29919,4853	195470,6046	239061,3453
Vd (L)	19,03	6,88	3,03
K_{el} (/minute)	0,01142	0,0088	0,0052
$t_{1/2}$ el (minute)	147,56	735,31	411,05
Cl (L/minute)	0,21732	0,06739	0,016048

The value of the elimination rate constant and the resulting elimination half-life are the same as the value of the elimination rate constant and the elimination half-life of theophylline in conventional tablets (between 6 to 12 hours), this indicates that these parameters are not affected by the dosage form.

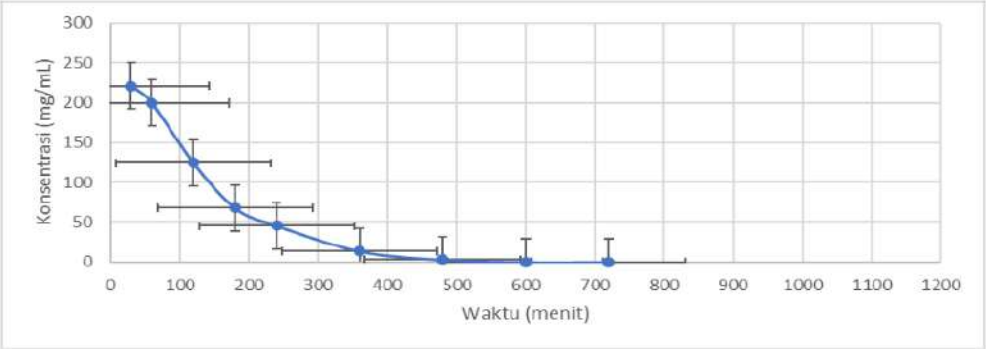

Figure 4.6 Plasma concentration profile i.p Sodium Valproate in rats (n=6)

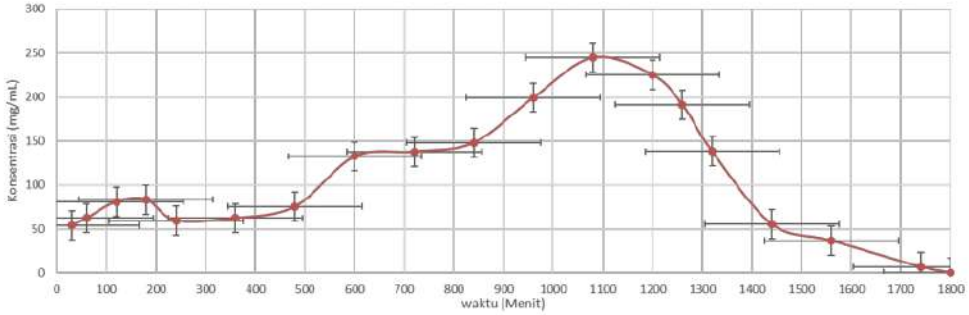

Figure 4.7 Plasma concentration profile of Valproate ER Tablets of Sodium in rats (n=6)

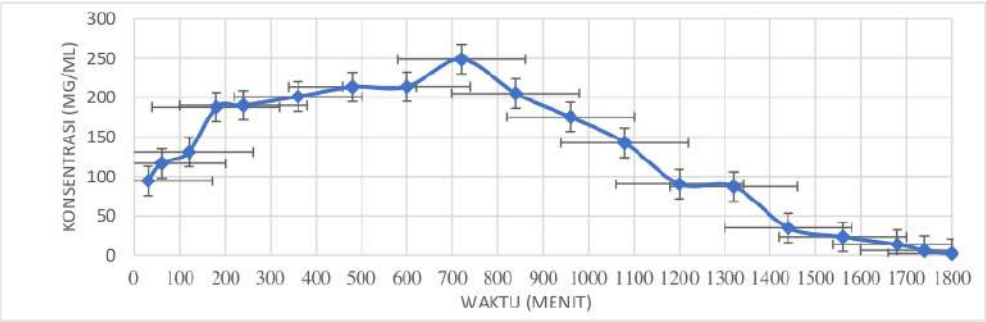

Figure 4.8 Mucoadhesive film buccal plasma concentration profile of Sodium Valproate in rats (n=6)

DISCUSSION

CONCLUSION

It was concluded that antiepileptic therapy was very effective with clearing of clearance

5. Patents

There is no patent resulting from the work reported in this manuscrip

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Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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REFERENCE

Ismail, Isam, Jafer I, Tamimi J. Determination of glimepiride in human plasma by liquid chromatography electrospray ionization tandem mass spectrometry. J. Chromatogr B, 5. 2004 : 103-109.

Shargel, L. dan Yu, Andrew B.C. 2005. Biofarmasetika dan Farmakokinetika Terapan Edisi 2. Airlangga University Press. Surabaya.

Tarek S. Belal, Dina S. El-Kafrawy, Mohamed S. Mahrous, Magdi M. Abdel-Khalek, Amira H. Abo-Gharam, 2016, Validated spectrophotometric methods for determination of sodium valproate based on charge transfer complexation reactions, Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 155 (2016) 47–53

Fisher, R.S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J.H., Elger, C.E., Engel, J Jr., Forsgren, L., French, J.A., Glynn, M., Hesdorffer, D.C., Lee, B.I., Mathern, G.W., Moshé,

S.L., Perucca, E., Scheffer, I.E., Tomson, T., Watanabe, M. And Wiebe, S. 2014. A Practical Clinical Definition of Epilepsy, Epilepsia, 55(4): 475-482

McNamara, J.O. 1999, ' Obat-obat yang Efektif Dalam Terapi

Ergul Erkec, O. (2015) 'Pentylenetetrazol Kindling Epilepsy Model', *Journal of the Turkish Epilepsi Society* [Preprint]. Available at: https://doi.org/10.5505/epilepsi.2015.08108.

Perucca, E. (2002) 'Pharmacological and Therapeutic Properties of Valproate', *CNS Drugs*, 16(10), pp. 695–714. Available at: https://doi.org/10.2165/00023210-200216100-00004.

Pinder, R.M. *et al*. (1977) 'Sodium Valproate: A Review of its Pharmacological Properties and Therapeutic Efficacy in Epilepsy', *Drugs*, 13(2), pp. 81–123. Available at: https://doi.org/10.2165/00003495-197713020-00001.

Virmani, T. *et al*. (2015) 'Buccal Drug Delivery system- Approach to Improve the Bioavailability', p. 7.

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