# Adverse reaction and rational use of paracetamol tablets and its drug content detection based on spectral test

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**Abstract**: Paracetamol and amantadine hydrochloride tablet is a commonly used drug to relieve the common cold. Its main ingredient is 4-Acetamidophenol. The safety of acetaminophen containing cold drugs has attracted more and more attention in recent years. In order to promote the clinical safety of drugs, the adverse reaction and clinical application of acetaminophen drugs are analyzed in this paper. The adverse reactions induced by acetaminophen mainly include: allergic reaction (46.1%), liver and kidney injury (25%), blood system (15.7%) and digestive system (5.2%). At the same time, we tested the content of acetaminophen by using spectral test. It can be seen that the method can be extended to the quantitative analysis and quality control of the effective components of other compound drugs.

**Keywords**: Drug content detection, adverse drug reaction, near infrared spectroscopy, paracetamol.

## INTRODUCTION

Paracetamol is the antipyretic analgesic. It is the main metabolite of phenacetin, is acetanilide derivatives, and is mainly used for non prescription drugs (OTC) antipyretic analgesic (Kosnett *et al.,* 2007; Cabaravdic *et al.,* 2010; Faramawi *et al.,* 2015). The drug plays an important role in regulating body temperature and analgesia by inhibiting the epoxide (COX) required by the synthesis of prostaglandin (Kuo *et al.,* 2006; Lu *et al.,* 2015). Acetaminophen, except for unilateral, is also made of compound preparation with other drugs, commonly used in the anti-cold treatment. Excessive use of acetaminophen can cause liver toxicity, and even lead to liver failure and death (Glenn *et al.,* 2003; Fang *et al.,* 2017). The safety of paracetamol cold medicine has attracted wide attention in recent years (Wu *et al.,* 1996; Weisskopf *et al.,* 2009; Poreba *et al.,* 2011). In order to promote the clinical safety of drugs, the adverse reaction and clinical application of acetaminophen drugs are analyzed in this paper.

The pharmacological action of acetaminophen is antipyretic and analgesic without anti-inflammatory effect. The following matters should be paid attention to when using medicine: (1) Attention should be paid to the careful reading of drug instructions before taking drugs. Besides taking the prescribed dose and interval time, attention should also be paid to the matters needing attention, adverse reactions, contraindications and drug interactions. (2) It is forbidden to take this medicine in a large dose of the cold time and abdomen in the cold time, and it is forbidden to take this medicine after drinking. (3) Understand the specific ingredients of all kinds of cold drugs on the market and avoid taking 2 or more than 2 kinds of cold medicine containing acetaminophen.(4)For elderly patients, in order to reduce the risk of gastric and duodenal bleeding and kidney, the dosage should be reduced by 30%-40% (Glenn *et al.*,2006; Hara *et al.*,2015; Liu *et al.,* 2017), lactating women and children should be given the prescribed dose during fever, and the interval between them should be more than 6 hours, so as to avoid long-term use (Neri *et al.,*1988; Li *et al.,* 2015). (5)It should be avoided for liver function insufficiency, renal function damage, anemia, heart failure, severe coronary heart disease, pulmonary heart disease, pregnant women and neonates (Park *et al.,* 2009).

Acetaminophen determination method is mainly used in high performance liquid chromatography (HPLC) method, and capillary gas chromatography, TLC, spectrophotometry, sodium nitrite, external standard method, these methods require sample pretreatment, and organic reagents, and time-consuming, complicated operation tedious(Staessen *et al.,* 1996; Peters *et al.,* 2012; Eum *et al.,* 2011; Hara *et al.,* 2015). This paper uses near infrared spectroscopy scans for compound paracetamol and amantadine hydrochloride solid samples, and samples of near infrared spectroscopy and the sample in the regression analysis between acetaminophen content using partial least squares method has strong nonlinear analytical ability, performance robust and predictive model (Bushnik *et al.,* 2014; Cosselman *et al.,* 2015). The method has the advantages of convenient and quick, no need to pretreat samples and no other organic reagents. It is expected to be one of the conventional methods of drug analysis. Near infrared reflectance spetroscopy (NIRS) is a new technology for quickly estimating the content of one or more chemical components in samples by using the optical properties of organic chemicals in their near-infrared spectral region (Ostojic *et al.,* 2015; Poręba *et al.,* 2011).

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***Acetamidophenol***

Paracetamol and amantadine hydrochloride tablets is commonly used to relieve fever, caused by the common cold or influenza headache, stuffy nose, sore throat; antiviral; anti infection; can also be used for non prescription drugs for prevention and treatment of influenza, the main component of acetaminophen (4-Acetamidophenol, $C_8H_9NO_2$), the structure shown in fig. 1, have antipyretic analgesic the role and its mechanism of action is the central regulation of prostaglandin through inhibition of hypothalamic temperature ($PGE_2$) synthesis and release from peripheral vascular expansion, in order to cause sweating antipyretic effect, and can inhibit the bradykinin, increase pain threshold and produce analgesic action.

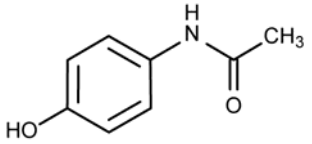


**Fig. 1**: Paracetamol molecular structural formula.

## MATERIALS AND METHODS

The clinical data of 76 patients with paracetamol induced adverse reactions were analyzed retrospectively. Among them, there were 43 males and 33 females. The age was 6~71 years, and the average age was (41.7± 2.1) years. This study was approved by the medical ethics committee of the Yangtze University, and the patient's knowledge and consent were obtained.

The main adverse reactions of acetaminophen in the digestive system include nausea, vomiting and abdominal pain. Excessive or long-term use of acetaminophen can cause liver damage and cholestatic hepatitis. Severe cases can cause liver coma or even death. Liver failure caused by liver damage is the most serious adverse reaction of this drug. In the respiratory system, paracetamol can lead to asthma attacks. The use of this drug in pregnant women can increase the incidence of asthma in infants. In the urinary system, excessive use of paracetamol can cause renal tubular necrosis, hematuria, and renal failure. Acetaminophen is a drug that induces potential thrombocytopenia in the blood system. It can cause immune hemolytic anemia, acute bone marrow hematopoiesis and methemoglobin. At the same time, acetaminophen can cause anaphylactic shock, skin urticaria with pruritus. It includes fixed drug eruption, bullous necrotizing epidermolysis and multiple organ damage.

## STATISTICAL ANALYSIS

The SPSS 17 statistical software was used to analyze the data. The measurement data is expressed as x± s, and Shapiro-Wilk test is used to detect data normality. Levene test or F test is used. Counting data is expressed by chi square. The difference of $P<0.05$ was statistically significant. The patch area changes before and after the treatment were measured by paired sample t test. The difference was statistically significant when the definition of $P<0.05$ was defined.

## RESULTS

***Type of adverse reaction***

76 cases of acetaminophen induced adverse reactions were mainly related to the system: allergic reaction, the percentage was 46.1%, the percentage of liver and kidney injury was 25%, the percentage of blood system was 15.7%, the percentage of digestive system was 5.2%, others were 7.8%. The specific situation is shown in table 1.

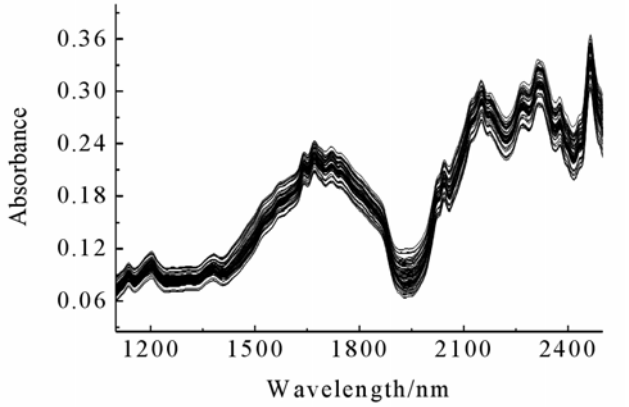


**Fig. 2**: Near infrared original Atlas of Comound Paracetamol and Amantadine Hydrochloride tablets samples

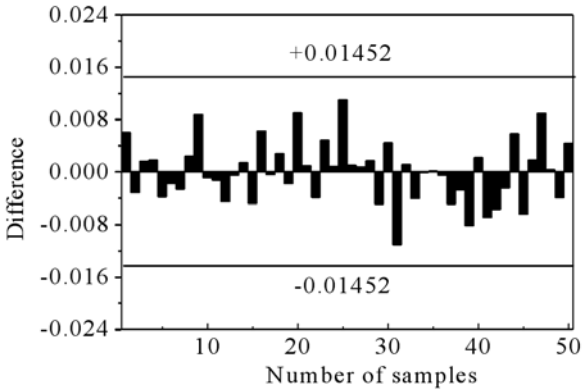


**Fig. 3**: **A**bsolute error between the predicted value and the chemical measured value

***Adverse reaction factors***

After statistics, the incidence of adverse reactions accounted for 56.6% of men, 35.5% of those under the age of 10 and 60.5% of drugs alone, accounting for 68.5% of the two consecutive times. The specific situation is shown in table 2. The irrational use of drugs is shown in table 3 Related to the drug situation as shown in table 4.

**Table 1**: Type of adverse drug reaction

| Involving systems | Cases | Percentage | Main types |
|---|---|---|---|
| Anaphylaxis | 35 | 46.3 | Drug rash, asthma, edema |
| Liver and kidney damage | 19 | 25.0 | Hepatocyte damage, toxic hepatitis and liver and kidney damage |
| Blood system | 12 | 15.7 | Hematuria, blood cell and thrombocytopenia, hemolytic anemia |
| Digestive system | 4 | 5.2 | Gastrointestinal bleeding and gastric hemorrhage |
| Other | 6 | 7.8 | Supraventricular tachycardia |
| Total | 76 | 100 | Multiple organ injury, abnormal psychosis, hypoglycemia coma |

**Table 2**: Analysis of related factors

| Factor | Type | Cases | Percentage |
|---|---|---|---|
| Gender | Male | 43 | 56.6 |
| | Female | 33 | 43.4 |
| Age | <10 | 27 | 35.5 |
| | 10-25 | 21 | 27.6 |
| | 25-50 | 17 | 22.3 |
| | >50 | 11 | 14.4 |
| Drug use | Single drug use | 46 | 60.5 |
| | Combined use of drugs | 30 | 39.4 |
| Adverse reaction | First time drug use | 24 | 31.5 |
| | After 2 times of medication | 52 | 68.5 |

**Table 3**: Irrational drug use

| Unreasonable situation | Cases | Percentage |
|---|---|---|
| The use of 2 or more drugs containing paracetamol at the same time | 28 | 36.8 |
| Overdose of drugs | 12 | 15.7 |
| Take the drug on an empty stomach | 17 | 22.9 |
| Take the medicine after drinking | 5 | 6.5 |

**Table 4**: Irr. involving drugs

| General-purpose name | Dosage form | Paracetamol content | Other main components |
|---|---|---|---|
| Compound Paracetamot and Amantadine Hydrochloride capsules | Capsule | 250 mg/ particles | Amantadine hydrochloride, Chlorphenamine Maleate |
| Compound Chlorzoxazone Dispersible Tablets | Dispersible tablet | 0.15 g/ slices | Chlorzoxazone |
| Compound Paracetamol and Dextromethorphan Syrup | Syrup | 15 mg. ml-1 | Dextromethorphan Hydrobromide and Methylephedrine Hydrochloride |
| Compound Paracetamol Tablets | Tablet | 0.25 g/ slices | Propyphenazone, Anhydrous Caffeine, Artificial bezoar |
| Vitamin C Yinqiao Tablets | Tablet | 105 mg/ slices | Vitamin C, Honeysuckle, Forsythia |

**Table 5**: Compound paracetamol and amantadine hydrochloride tablets sample concentration

| | Minimum value | Maximum value | Average value | Samples |
|---|---|---|---|---|
| Acetaminophen | 43.26 | 56.13 | 48.30 | 50 |

**Table 6**: Prediction set and correction set content of Compound paracetamol

| | Minimum value | Maximum value | Average value | Samples |
|---|---|---|---|---|
| Correction set | 48.13 | 54.26 | 43.75 | 35 |
| Prediction set | 51.27 | 53.05 | 45.61 | 15 |

**Table 7**: The performance parameters of PLS quantitative analysis model

| Spectral region | RMSECV | RMSEC | RMSEP | Rv | Rc | Factors |
|---|---|---|---|---|---|---|
| 1100~1320 | 0.00651 | 0.00306 | 0.00518 | 0.94611 | 0.98463 | 5 |
| 1320~1600 | 0.00682 | 0.00542 | 0.00691 | 0.97823 | 0.97512 | 4 |
| 1600~1899 | 0.00635 | 0.00382 | 0.00816 | 0.96570 | 0.97404 | 4 |
| 1899~2125 | 0.00592 | 0.00413 | 0.00548 | 0.97925 | 0.98124 | 3 |
| 2125~2399 | 0.00801 | 0.00421 | 0.00599 | 0.93821 | 0.96573 | 4 |
| 2399~2560 | 0.00884 | 0.00516 | 0.00876 | 0.92518 | 0.98052 | 5 |
| 1100~2800 | 0.00597 | 0.00452 | 0.00562 | 0.97619 | 0.97625 | 5 |

**Table 8**: Prediction results of paracetamol content

| Sample | Acetaminophen | | Sample Real value | Acetaminophen | |
|---|---|---|---|---|---|
| | Real value | Predicted value | | Real value | Acetaminophen |
| 1 | 0.4216 | 0.4258 | 7 | 0.5278 | 0.5416 |
| 2 | 0.4392 | 0.4410 | 8 | 0.5314 | 0.5408 |
| 3 | 0.4706 | 0.4759 | 9 | 0.5297 | 0.5124 |
| 4 | 0.4850 | 0.4644 | 10 | 0.4975 | 0.5042 |
| 5 | 0.5014 | 0.4975 | 11 | 0.4951 | 0.4978 |
| 6 | 0.5123 | 0.5049 | … | … | … |
| Average value | Real value =0.514766; prediction value =0.503568 | | | | |
| RMSEP | 0.00427 | | | | |

***Measurement of drug concentration***

At the same time, we measured the concentration of acetaminophen in the drug concentration. The drug named paracetamol and amantadine hydrochloride tablets has the highest adverse reaction ratio in the retrospective case, so we selected and measured the content of paracetamol of this drug. According to the formula of paracetamol and amantadine hydrochloride tablets, we prepared 40 paracetamol and amantadine hydrochloride tablets powder samples, the content of acetamidophenol ranged from 44.989% to 55.010%. Other ingredients were adjusted according to the formula. To purchase 10 different batches of paracetamol and amantadine hydrochloride tablets, take 5 pieces and grind them as actual samples. The measured values are taken as real values. The results of 50 samples and the content values measured by actual samples are shown in table 5.

The acetaminophen reference substance was dried at 105 °C , and the reference substance was 25 mg. Then it was placed in 25 m L volumetric flask. Diluted with mobile phase to scale, shake up the product. The control product was accurately moved 1.0, 1.5, 2, 2.5, 3 m L, and placed in a 25 ml capacity bottle, which was fixed to the scale by the flow phase.According to the above chromatographic conditions, the peak area of acetaminophen was determined by injection of 20 μL, and linear regression was carried out with reference solution concentration as abscissa and corresponding peak area as ordinate. ake 5 tablets of each batch of Comound Paracetamol and Amantadine Hydrochloride tablets, precision grinding, take an appropriate amount, with the mobile phase is dissolved and diluted diluted to about 25 g/m L solution, and immediately take 20 μL injection liquid chromatograph, record peak area, into the standard equation to calculate the content of paracetamol.

***Analysis of the original spectrum of the sample***

The original near infrared spectra of 50 samples of paracetamol and amantadine hydrochloride tablets as shown in fig. 2, can be seen from fig. 2 the original NIR spectra of paracetamol and amantadine hydrochloride tablets samples near infrared region weak absorption peak, more complex, severe spectral overlap, general linear regression analysis to analysis, this paper uses partial least squares (PLS), establish the relationship between the spectral data and the acetyl amino phenol content, and can eliminate the redundant information among data, achieve the purpose of dimension reduction. At the same time in order to extract information, instrument drift and remove interference and baseline background caused by the effective spectrum caused by noise were investigated using convolution smoothing, Fu Liye transform, first derivative and two derivative spectra pretreatment method for spectral preprocessing, in order to establish a robust and quantitative analysis the content of paracetamol has good prediction ability in the determination of paracetamol and amantadine hydrochloride tablets.

The spectral data of samples were verified by interaction. The absolute error between predicted values and chemical measurements obtained by mutual validation is shown in fig. 3. The absolute error is 0.00363, use 4 times of this value, ± .01452 as the field value of outliers. As can be seen from fig. 3, all the samples are not beyond the value of the domain, and all the samples can be applied to the built model.

And prediction samples affect the selection of prediction model robustness and generalization ability of the model in the correction of component content within the range of stability prediction is a good guarantee, principal component analysis for low dimensional data compression spectrum, near infrared spectrum of the original complex into simple spectra of various elements, and removal the disturbance component and interference factors, the main information spectra of the main reaction in the first and the second principal components, samples and prediction samples and correction of rational choice. The contribution rate of the two principal components was 95.12%, 2.45% and 97.57% respectively. It represents the main information of the spectrum, indicating that other interfering factors have less influence on the spectrum.

***Other methods of measurement***

The original spectra were investigated, convolution smoothing spectrum, fast fourier transform (FFT) spectra, first derivative spectra and two derivative spectra based on different spectral region analysis model of determination of the content of paracetamol in Comound Paracetamol and Amantadine Hydrochloride tablets PLS quantitative, each model through internal cross validation, using RMSECV as the evaluation criteria, the most main factor suitable choice of number, the optimal model of various spectrum established, the performance parameters of the optimal model of two order derivative spectra are established in the 1100~2121 nm spectral region were the best. The model was used to predict the content of acetaminophen in the predicted samples. The real and predicted results were listed in table 8 and the real and predicted values were tested by bilateral t. The results showed that there was no significant difference between the real value and the predicted value.

## DISCUSSION

Acetaminophe is very effective in antipyretic and analgesic effect, but its anti-inflammatory effect is weak. But it is generally considered safe in clinical practice, so it is widely applied in the treatment of cold, fever, neuralgia, postoperative pain and joint pain (Poręba *et al.,* 2010; Taheri *et al.,* 2014). It is absorbed very quickly after application and can be evenly distributed in the body after absorption. But more and more recent reports of adverse reactions to acetaminophen have been reported (Rapisarda *et al.,* 2015; Wildemann *et al.,* 2015). In the analysis of the related factors of the above adverse reactions, we can see that the proportion of patients aged 12~59 years is the highest (Were *et al.,* 2014). The reason may be that the number of patients in this age group is quite large, and there are many opportunities for their medication. The doses of acetaminophen, is required in accordance with the following criteria: adult <2g/day, the antipyretic treatment must be less than 3 D, the analgesic treatment is less than or equal to 10 days (D); under the age of 12 patients were 50~75 mg/(kg·times), the course of treatment was less than 5d. The dosage of infant was 10~15 mg/ (kg·times), and it could also be administered according to the body surface area of children. The dosage was 1.5g/ ($M^2$·d), and the times were 4~6 h/ times. In these patients, one of the patients took 78 paracetamol orally, with a dose of 39 g, and subacute liver necrosis after 5 h of the drug. Therefore, when taking acetaminophen, it must be strictly controlled to reduce the occurrence of adverse reactions. In acetaminophen induced liver injury, alcohol is also one of the main influencing factors (Kosnett *et al.,* 2007; Cabaravdic *et al.,* 2010). If it is drinking during the period of taking medicine, even if the dosage is very small, it will also lead to a moderate dose in a short time, resulting in poisoning. Therefore, when taking acetaminophen, it is not suitable for drinking. Chronic alcoholism is one of the main risk factors for acetaminophen liver injury. Therefore, it is necessary to eliminate alcohol consumption during the period of taking medicine, so as to reduce the occurrence of liver damage.

The use of acetaminophen in children has also been reported, and the safety of drug use in children has become one of the focus of attention (Staessen *et al.,* 1996; Peters *et al.,* 2012). The cold medicine containing acetaminophen is an over-the-counter drug, but it should be used cautiously with the increase of its reported adverse reactions, so as to avoid long-term high-dose use in order to prevent liver damage. Children's medication should try to choose children's special drugs or carefully read instructions about children's usage and those with renal insufficiency should try to reduce or use caution when using paracetamol as an anti cold medicine. During the drug use, pay attention to the response of the patient, such as discomfort and timely treatment (Faramawi *et al.,* 2015). The irrational use of drugs for children is the use of super dose and the choice of adult drugs for children. The drug was overdosed with two kinds of drugs containing acetaminophen. Repeat medication, for acetaminophen containing drugs and other analgesics used in combination, such as acetaminophen containing drugs and nimesulide; there are other unreasonable drug combination, drinking and other issues. It is suggested that clinical medication should be used rationally according to the patient's condition, individual difference, drug characteristics and application principles of antipyretic drugs. Drug dosage should not be too large, drug time should not be too long, not frequent replacement of drugs, more than the same use of two or more than two kinds of such drugs.

At the same time, the content of paracetamol in compound paracetamol and Amantadine Hydrochloride tablets was measured by NIRS-PLS in this paper (Faramawi *et al.,* 2015). The method can be extended to

other compound drugs and neutralize the quantitative analysis and quality control of effective components of traditional Chinese medicine (Staessen *et al.,* 1996, Peters *et al.,* 2012). Establish the quantitative analysis model of the content of paracetamol and Chinese medicine shikimic acid content determination of anti viral medicine Compound Paracetamol and Amantadine Hydrochloride tablets application of near infrared diffuse reflectance spectroscopy combined with PLS method (Eum *et al.,* 2011), the new method does not need to sample for chemical treatment, convenient and quick; PLS can better analysis of near infrared diffuse reflectance spectra overlap phenomenon; to solve the interference problem of components; prediction quantitative analysis of Compound Paracetamol and Amantadine Hydrochloride tablets precision can meet the requirements of the production process. Near Infrared Reflectance Spetroscopy is a new technology for quickly estimating the content of one or more chemical components in samples by using the optical properties of organic chemicals in its near-infrared spectral region. It has the advantages of fast, convenient, simple, accurate and simultaneous analysis of various components (Hara *et al.,*2015). After the spectral preprocessing and spectral selection, quantitative analysis model was established for determination of paracetamol in paracetamol and amantadine hydrochloride tablets and the root mean square error of cross validation (RMSECV) as the evaluation index, the establishment of each model is the optimal principal factor number selection, results show that the near infrared two order derivative spectra based on the 1100~2121 nm spectral region in the determination of paracetamol in the model is the optimal model. The results show that the method is feasible, convenient and quick, without pre processing, and can be detected online, without destruction, and has a great application prospect.

## CONCLUSION

In order to further understand the clinical application and adverse reactions of acetaminophen in clinical practice, and to better guide clinical safety and rational application and reduce the occurrence of drug damage events, we should increase sample monitoring so as to comprehensively evaluate the safety of these drugs.

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